

American Gynecological Society

OFFICIAL REPORTS OF THE
REFERATS

FORTY-SECOND ANNUAL MEETING

PITTSBURGH, PA., MAY 31, JUNE 1 AND 2

1917

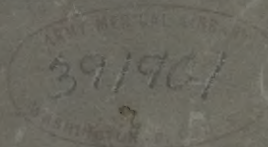
THE RELATION

OF THE

GLANDS OF INTERNAL SECRETION

TO

GYNECOLOGY AND OBSTETRICS



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annex

PREFACE

THE American Gynecological Society decided in 1916 to prepare a Referat on "The Relations of the Glands of Internal Secretion to Gynecology and Obstetrics" for its June meeting in 1917. The selection is most timely because the subject is of ever-increasing interest both to the specialist and the general profession. In contradistinction to the glibness with which the terms "disturbance of internal secretion," "polyglandular syndrome," "hyper-, hypo- or dysfunction" of this or that ductless gland are applied, the basic conceptions held of the physiological and pathological action of the endocrine glands are often most vague and inaccurate.

Much of this confusion is due to the flood of superficial clinical and experimental articles appearing daily in the literature. These ephemera merely becloud the issue, and serve to distract both the initiate and uninitiate. By mere force of number, they hide the occasional article of merit. In consequence, encyclopedic compendiums such as those of Biedl and Falta, in which an attempt to sift and critically examine the material is made, largely fail to attain their purpose. The mass of literature is overwhelming; too big to be more than codified by a single editor. Each gland may well be selected as a life's work, and the application of our knowledge to various medical groupings—such as gynecological, neurological, psychological, metabolic, etc., etc.—deserves equally intensive study.

In order to present to the Society, and later to the pro-

fession at large, as accurate and authoritative a view, as the present state of our knowledge will permit, of the relation of the glands of internal secretion to the female generative tract, the committee has enlisted the assistance of a number of distinguished workers, with the object of having each contributor undertake a survey of his special field. The articles which follow, as well as the additional papers which will be read at the June meeting, are designed to cover the subject with sufficient completeness to present to the clinician a condensed and clarified view of a most intricate and involved subject still in its formative stage.

THE COMMITTEE:

ROBERT T. FRANK, New York,
Chairman.

WM. P. GRAVES, Boston.

WM. H. MORLEY, Detroit.

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Ovarian Transplantation. FRANKLIN H. MARTIN, M.D., Chicago, Ill.

The Influence of Minor Alterations of the Ovary on General Health and their Relief by Surgery. EDWARD REYNOLDS, M.D., Boston, Mass.

INTRODUCTION

BY ROBERT T. FRANK, M. D.
New York

THIS introduction is written with the aim of bridging some of the gaps which of necessity occur in a symposium prepared by several independent investigators, who are obliged to confine their remarks to particular and limited fields. A cursory survey of the entire subject may, therefore, serve a useful purpose.

When the study of the glands of internal secretion was in its infancy, only arresting and striking facts, such as the amenorrhea and ablation symptoms following castration, or gross abnormalities which could not be overlooked, such as premature sexual ripening, attracted the attention of the gynecologist and obstetrician. Today, on the contrary, many minor changes in the appearance, behavior or physique of the patient are ascribed to the endocrine organs. If anything, this tendency to at once apply clinically the knowledge obtained by degrees at the bedside, the post-mortem table and in the laboratory threatens to mislead and to bring discredit upon an important branch of medical science.

In every department of knowledge it is expedient, at intervals, to stop, examine and meditate, to "take stock," so to speak, of closed, open and future prospects. Let this be such an occasion.

Femaleness is an attribute of woman, possessed in vary-

ing degree by individual members of the sex, primarily designed to foster the continuation of the race. Just as determination of sex is decided in the ovum, perhaps even before fertilization takes place, so the future fertility or sterility of the individual is often determined during infancy or before puberty.*

In order to comprehend the problems which confront us, it is necessary to trace the influence of the glands of internal secretion from the time of conception and follow it through senescence. A thorough study of this sequence is still frustrated by the incompleteness of our knowledge.

INFLUENCE OF THE GLANDS OF INTERNAL SECRETION: NORMAL EFFECTS

In Utero. That the maternal sex glands or gonads are not indispensable to the fetus after the fertilized ovum is firmly fixed in the uterus, has been repeatedly proved by the birth of perfect children, born of mothers castrated early in pregnancy (Essen-Moeller, Orgler, etc.). That the influence of some of the maternal glands is not entirely negligible, is shown by abnormalities sometimes noted in children born of mothers with diabetes, hyperthyroidism and tetany. This apparent variability may perhaps be accounted for by the fact that at least some of the glands of internal secretion probably begin to functionate early in fetal life. Among those investigated are the pancreas (Carlson), adrenal (Hoskins, Fenger) and thyroid (Halsted). The possibility of determining the influence of the

* The degree of femaleness, of feminine attributes, can be influenced by experimental methods. Steinach has made male guinea-pigs feminine in psyche, breast development, etc., by implanting ovarian tissue; Riddle has made doves either overfeminine or overmasculine in their behavior and characteristics by injecting homologous ovarian or testicular material. The possible bearing of these experiments on the subject of homo- and heterosexuality is self-evident.

gonad of the embryo has now been brought within measurable reach of experimental proof by Swift's observation that the germ cells of the chick, at an early stage, lie upon the yolk sac separated from the embryo, and may be removed without necessarily killing the embryo (Swift, Reagan). Our knowledge of this subject is as yet quite incomplete.

Postpartum. Immediately after birth the sex organs and breasts of both male and female children are larger and may show a degree of stimulation (uterine bleeding, colostrum), which disappears within two to three weeks postpartum. This hyperplasia has been ascribed by Halban to stimulating substances derived from the maternal placenta.

Infancy and Prepuberty. During infancy Graafian follicles develop to a certain degree and then regress. The ovaries must exert some influence during this period, because early castration in animals produces "eunuchoid" types, characterized by undeveloped sex organs and changes in the height, bony skeleton and in the glands of internal secretion. The opposite extreme is noted in those rare instances, in which premature sexual development occurs without gross lesions (Lenz). What influence is played by the so called "puberty glands" (thymus and pineal) in favoring or inhibiting sexual maturity is uncertain.

The developmental period is of critical importance to the individual, because anomalies directly ascribable to the stage of pubescence are noted with great frequency in the mature individual. These variations from the normal may manifest themselves in apparently disconnected phenomena, such as external appearance (height, facies, hair growth), in the internal economy (pelvic bones, genitals), in the degree of resistance to infection or disease, and in the soul life and intelligence. The exact mechanism by

which normal development and variations from the normal are produced is far from clear. Much of the obscurity is due to the almost inextricable interaction of the various glands which so far, in the main, defies analysis.

Sexual Maturity. In the human female the onset of maturity, which is a gradual process, usually evidences itself by a series of related phenomena. Popularly the best known is the appearance of menstruation. This coincides with the full development of a Graafian follicle, and is followed by rupture of the follicle and consequent corpus luteum formation, a gland, which, among other functions, regulates the periodicity of menstruation (L. Loeb). From then on, during complete health, unless disturbed by pregnancy, cyclical changes occur in the ovary and uterus, and, at least in certain individuals, in the breast, until the onset of sexual senescence. Some evidence obtains that other glands of internal secretion, in addition to the ovary, participate in the cyclical changes to a varying degree. Among them are the adrenal and the thyroid.

The onset of maturity is also marked by the completion of development of the secondary sexual characters, some primarily designed as sex allures, others having direct bearing upon the procreative function. Among the female secondary sexual characters of the first class are fineness and distribution of the hair, development and distribution of subcutaneous fat, gracile larynx with high pitched voice and feminine psyche; among those of the second class, of chief importance, is the development of the pelvis with large cavity and broad outlet.

The coincident involution of the thymus and pineal gland, and the enlargement of the thyroid are not fully understood.

Pregnancy not only produces local changes in the sex organs (cessation of the cycle with persistence of the

corpus luteum, growth of the uterus, formation of the placenta, hyperplasia of the breasts), but, likewise, exerts a profound influence upon the entire organism. Of the glands of internal secretion, the hypophysis undergoes the most manifest alteration (Erdheim and Stumme). Variations in function of the adrenal, thyroid, parathyroid and pancreas are not uncommon. Elaboration of this phase of the subject is not indicated in this connection.

Sexual Senescence (menopause). This period apparently coincides with the permanent cessation of follicle ripening. The ovaries no longer functionate and consequently atrophy of the internal and external genitals and of the breasts supervenes. There may be changes in the alterable secondary sexual characteristics—fat and hair distribution, psyche. Alterations in the other glands of internal secretion probably occur, but are not well understood.

This cursory résumé attempts to give in broad outline the main phases which occur from the onset of fetal development to old age in the life history of the normal female. Keeping in mind this standard, we will be in a better position to recognize variations from the normal.

INFLUENCE OF THE GLANDS OF INTERNAL SECRETIONS: VARIATIONS FROM THE NORMAL

Before ascribing symptoms arising in the generative tract to disturbances of the internal secretions, it is necessary to rule out other possible etiological factors. Only after such local or general causes have been excluded, should the glands of internal secretion be considered. It is impossible to state whether other glands of internal secretion besides the ovaries can exert a *direct* influence upon the genital tract. This much, however, is clear, that

no matter what the origin of the stimulation or depression may be, the symptoms produced are identical with symptoms arising from primary stimulation or depression of ovarian function. The functional manifestation, whether of hyperfunctional or hypofunctional nature are often but not invariably dependent upon anatomical changes in the uterus, vagina and external genitals. No characteristic anatomical changes have as yet been detected in the ovaries. The anatomical changes, and, consequently, the functional disturbances also, may be transitory or permanent.

HYPOFUNCTION

Hypofunction may be primary or secondary. The foundation for *primary hypofunction* is often laid in the prepuberty period. Therefore, *a. unalterable developmental stigmata* may be noted—bone changes (long extremities, short trunk, flat sacrum, narrow pelvic outlet), as well as changes in *b. alterable secondary sex characters*—hair and fat distribution (of eunuchoid or male type). *c. Nervous symptoms* are frequent, either general hyperexcitability or stolidity, and instability of the vasomotor system marked by sweats, flushes and dizziness. *d. Permanent local stigmata* may be summarized under the head of hypoplastic infantilistic genitals; while the type of transient hypoplasia is illustrated by “lactation atrophy.” Symptomatically hypofunction is exemplified by sterility, amenorrhea, scant, irregular and painful menstruation.

Secondary hypofunction occurs most commonly in consequence of thyroid (exophthalmic goitre, myxedema), hypophyseal (acromegaly, dystrophia adiposogenitalis), adrenal medullary (Addison's) disease, etc. Often after a transitory period of hyperfunction, uterine atrophy sets in (amenorrhea, sterility).

HYPERFUNCTION

Primary hyperfunction, with few exceptions, is a disease limited to the period of sexual maturity. At the beginning (puberty) and end (prelimacteric) of this period hyperfunctional manifestations may be severe. The cardinal symptoms are menorrhagia and metrorrhagia. The uterine mucosa is often hyperplastic, and in many cases the uterine musculature is thickened (metritic type). Some evidence obtains that uterine fibromyomata are the result of functional hyperplasia.

Secondary hyperfunction is most often noted as a transitory phenomenon at the onset of some diseases of other glands of internal secretion (exophthalmic goitre, etc.). It may also result from local stimulation of the ovaries due to inflammation or tumors.

DIAGNOSIS

Routine diagnostic methods as practiced at the present day in the office, dispensary and wards of the hospital will not advance our knowledge of the course of those diseases of the glands of internal secretion which produce gynecological and obstetrical symptoms. Not until thorough and complete studies, conducted by groups of workers, are begun and persevered with, may we hope for concrete gain. The clinical material floods our institutions, hidden under the guise of sterility, dysmenorrhea, "neurasthenia," "retroflexion," menorrhagia, metrorrhagia, etc., unclassified, unstudied, unrelieved. Pathologist, pharmacologist and biological chemist must be enlisted in this work to coöperate with the clinician. Then, and then only, may tangible results be expected. No advance in diagnosis can be recorded since the writer presented the subject before the members of the Society in May, 1914.

ORGANOTHERAPY

Little, if any advance in this branch of medicine is to be recorded in the last years.

Kendall has announced the discovery in crystalline form of the active principle of the thyroid gland. The method of preparation of this product has not yet been published in detail, nor have the reports on its physiological activity been conclusive. Therefore, this discovery, which, if confirmed, will prove of the utmost importance, is still *sub judice*.

The usual number of reports on the use and effects of corpus luteum extracts have appeared in the literature. All those commercial extracts (and these are the extracts which were employed in the clinical articles reported), which the writer has examined, have proved inactive biologically, using the growth effect exerted on the rabbit uterus as a test. No further reports on the general pharmacological activity of corpus luteum are on hand.

The sole organotherapeutic preparation which can be relied upon is thyroid extract. Its use in gynecology and obstetrics, except in cases of gross deficiency of the thyroid secretion, is still largely empirical.

Both pituitrin and adrenalin are hormones which exert purely local drug effects,* and do not replace the functional activities of the glands from which they are derived. Therefore, their exhibition is very limited. The extracts of anterior lobe pituitary, pineal, thymus and adrenal

* The apparently complex action of adrenalin, which inhibits the motion of the small intestine, stimulates contraction of uterine muscle, dilates the bronchi, etc., is explained by the fact that the drug acts as a stimulant of the myoneural junctions of the sympathetic system and, therefore, produces the effect of general stimulation of sympathetic fibers. As these fibers act partly as inhibitors, partly as excitors of different viscera, most diverse effects may be expected and actually occur.

cortex (desiccated adrenal) now obtainable and in the dosage now employed show no, or only unconvincing, effects.

If the hormone theory as accepted at present and in proof of which so much correlated data have been accumulated in both the clinic and in the experimental laboratory, eventually is to find practical application and usefulness in therapeutics, the "vital" principles of some of the glands of internal secretion must first be isolated, and the proper dosage and method of prescribing them must be discovered. Among these vital or essential glands should be classed the anterior lobe of the pituitary, the parathyroids, the adrenal cortex and pancreas. Neither the thyroid, thymus, pineal, ovary or testis are essential to the continuance of life, although their secretions play a rôle of variable importance in the organism, a rôle not necessarily at once apparent after their ablation or atrophy.

According to our concepts of physiology, specific cells produce only specific secretory products, so that while we may conceive that the cells of the gastric glands produce greater or lesser amounts of hydrochloric acid, we cannot conceive of their secreting lactic acid, for example. Analogously, we may accept that the specific cells of a given gland of internal secretion can elaborate one or more specific products, that this secretion may vary in amount or concentration, but not that it may vary in character. If anything more than this variation in amount, concentration or rate of discharge into the blood stream, and such variations should be capable of producing the most diverse phenomena, is implied by the term "dysfunction," this term lacks all theoretical or experimental basis and should be dropped from medical terminology.

By discarding "dysfunction," the problem is much simplified. A hormone may then be regarded as the specific product of a secretory cell, and a given type of cell

can then be expected to produce only one (or more) secretion. Such specific secretory products as we understand most clearly, produce distinct *drug actions*, which may be simple and rapid as that of adrenalin, which stimulates the sympathetic nervous system, or more slow and less immediately apparent in its effects as thyroid substance, which increases the rate of metabolic activity. In any case, a potent hormone derivative should have a pharmacological activity, *which lends itself to standardization, and which can be demonstrated by biological tests*. Until this entire concept is grasped and applied, our efforts at organotherapy will remain in their present state of crude empiricism in exact parallelism with the crudity of diagnosis in disease of the glands of internal secretion.

THE RELATION OF THE PITUITARY GLAND TO THE FEMALE GENERATIVE ORGANS

FROM THE EXPERIMENTAL AND CLINICAL ASPECTS

BY EMIL GOETSCH, M. D.
Baltimore, Md.

IN view of the great interest which is being manifested more and more and because of the interesting and almost startling revelations which are accumulating in the field of endocrinology, it is desirable that investigators and clinicians should at all times be able to distinguish between facts and theories in regard to the interrelationship of the ductless glands. There is great danger in discussions of the physiology and pathology of these organs to engage in fruitless theorization and suggestions unless there is a firm basis of well-controlled experimental and clinical observations to stand upon. On the other hand, one should preserve a mind open to suggestions and "leads" which are constantly being met with in studies on the ductless glands, and should not approach the subject in too critical a manner, simply because our knowledge of endocrinology at the present time is still very limited.

Many facts have been discovered which have aided us materially in understanding the involved syndromes met with in clinical cases exhibiting evident ductless gland disturbances. Particularly from the laboratory have come many enlightening discoveries and suggestions which have

cleared away the confusion surrounding the diagnosis and treatment of those unfortunate individuals who show the consequences of disturbances in their endocrine glands, and who are appearing for treatment in constantly increasing numbers.

1. GROSS AND HISTOLOGICAL STRUCTURE OF THE PITUITARY GLAND

GROSS. We have become more and more intimately acquainted in recent years with clinical evidences of disturbed function of the hypophysis. This gland, also called the pituitary body, is thoroughly protected by nature in being centrally located at the base of the skull and surrounded by a bony encasement called the sella turcica. It consists of the anterior or glandular part, which is considerably larger than the posterior or nervous part, and gives the gland its characteristic pinkish-grey appearance in the fresh condition. The anterior epithelial part is further divided into the large "pars anterior" proper, which constitutes about three-fourths of the gland and presents a pinkish-grey appearance, and the posterior narrower zone of whitish appearance, called also "pars intermedia." The latter constitutes the epithelial lining or encasement of the posterior lobe, and extends upward along the infundibulum frequently even to the floor of the third ventricle. Between these two divisions of the epithelial or glandular portion lies the cleft, the embryonic remains of the original cavity of Rathke's pouch.

HISTOLOGICAL. There are two fundamentally different types of cells in the anterior lobe depending upon their affinity for stains, the chromophilic which stain intensely with either the acid or basic stains and contain secretion granules, whereas the chromophobe have no special affinity for either basic or acid dyes and are non-granular. The

pars intermedia which invests the posterior lobe is composed of several layers of undifferentiated cells without blood vessels or connective tissue stroma. These cells elaborate a kind of colloid secretion which is thought by some to find its way through the meshes of the posterior lobe into the third ventricle of the brain. It is probably this colloid material which carries the active principle of these cells, often called "Pituitrin." The cells of the anterior lobe without doubt discharge their secretion directly into the large blood and lymph sinuses which are so numerous here and with which the cells are in such intimate contact.

Correlation between alterations in structure and function. Disturbances in pituitary function are associated with changes in these anatomical constituents of the normal hypophysis. Thus hyperfunction is associated with focal or general hyperplasias of the chromophil cells, while hypofunction is associated with certain degenerations, with atrophy and with tumor formation either of the hypophysis itself or as a result of pressure from tumors arising from a neighboring structure. Such pathological involvement of the gland is followed by symptoms of deficient glandular secretion as elsewhere in glandular organs.

II. INTERRELATIONSHIP IN FUNCTION BETWEEN THE PITUITARY GLAND AND THE FEMALE GENERATIVE ORGANS

It is my purpose to discuss in this paper our knowledge concerning the interrelationship between the pituitary gland and the female generative organs. Perhaps between no two of the ductless gland series is a clearer association in function demonstrable, a fact supported by many experimental and clinical observations. In this paper I shall discuss firstly, the former and then as a corollary to this shall consider secondly the clinical data bearing upon this subject. It seems desirable furthermore to consider prin-

cipally those facts which have been well controlled experimentally and clinically, and to mention only incidentally theoretical observations and suggestions.

A. EXPERIMENTAL EVIDENCE

A. PITUITARY DEFICIENCY. On account of its difficulty of attack in an experimental way the pituitary gland was the last of the ductless gland series to receive serious attention at the hands of laboratory investigators. Practically all of our knowledge concerning this small gland has been gained during the last ten years. The first series of experiments which showed that pituitary and sex functions were closely interrelated, was that reported by Crowe, Cushing and Homans,¹ who noted among many other changes that partial removal of the pituitary anterior lobe in dogs was followed by secondary hypoplasia of the organs of generation in adults, or by a persistence of sexual infantilism in case the operation was carried out on puppy dogs. There was a tendency to the disposition of fat much as seen in states of adiposity and of sexual infantilism in man. These changes following upon an artificially created deficiency of anterior lobe secretion are characteristic of both males and females.

It may here be interesting to mention some further striking results obtained by Aschner² who in 1912 published his findings after total and partial hypophysectomy in dogs. In adult animals there was observed a slight hypoplastic change in the sex glands and a definitely diminished sexual activity. In young animals the partial removal of the pituitary led to very marked and characteristic changes. There was an entire failure of development of the sex apparatus and of sexual activity in both males and females. The sex glands remained infantile in character. There was impotence and absence of spermatogenesis in the males and failure of ovulation and sexual instincts in the female. Furthermore hypophysectomy

during pregnancy caused abortion. There was also marked retardation in corporeal growth and diminished general activity of the animals thus operated upon. Other characteristics noted were a certain psychic depression, subnormal temperature, persistent puppy type of hair, a thick inelastic skin, persistence of the milk teeth, failure of closure of the epiphyses and a delicate and underdeveloped condition of the skeleton. Certain rather constant changes were also seen in the parenchymatous organs such as increased size of the colloid alveoli in the thyroid, an abnormally persistent thymus, fatty infiltration into the liver and increased thickness of the adrenal cortex. Aschner regards the anterior lobe as mainly responsible for these changes. The writer has been able to confirm these findings in numerous instances.

The occurrence of adiposity along with the sexual infantilism is probably a result of deficiency of posterior lobe secretion. In a report by Goetsch, Cushing and Jacobson,³ upon experiments conducted to determine the relationship of the hypophysis and especially of its posterior lobe and infundibulum to glycosuria, polyuria, and carbohydrate metabolism, they show that under various forms of operative manipulations of the infundibulum, hypophyseal stalk, and often of the posterior lobe itself a transient hyperglycæmia is produced with an associated diminution in the assimilation limit for ingested carbohydrates. In many instances a transient spontaneous glycosuria was produced.

If the operation had been so conducted as to create a subsequent and permanent insufficiency of posterior lobe secretion the temporary lowering of the assimilation limit is succeeded by an abnormal and enduring augmentation in the tolerance for sugars.

The assimilation limit for carbohydrates, greatly increased under these circumstances, can be promptly lowered by the coincident intravenous or subcutaneous injection of posterior lobe extract. This extract, furthermore,

has a pronounced effect in lowering the sugar tolerance of the normal animal, in whom it may even cause glycosuria when given in sufficient dosage.

B. EFFECTS PRODUCED BY PITUITARY EXTRACTS. In the foregoing we have considered the evidence obtained from experimentally created pituitary deficiency for believing that pituitary and sex functions are closely inter-related. The next step in the investigation is a natural one, namely, that of studying the results in animals, of the administration of fresh pituitary gland, dried extracts, fluid extracts or active principle in one way or another. For this purpose the hypophysis of various animals has been used, such as that of the ox, horse, cat, dog, sheep and even man. The source of the gland extract seems to have little effect upon the results, so long as the particular extract used is an active one. The results obtained by many investigators who have worked on these problems cannot be fully discussed here. The results of many of the earlier workers have subsequently been shown to be wrong because of failure to distinguish between the extracts of the anterior and posterior lobes, whose properties we now know are distinct and different. Then again proper attention was not given to the question of dosage. We now know, for example, that a dose which was administered to a young animal over a considerable period of time and which was obviously too large produced toxic effects and gave results precisely opposite to those obtained by other workers using small stimulating doses. Great difficulty was at first experienced in standardizing the strength of the extracts used, as a consequence of which investigators reported varying results following the use of extracts of varying strength.

Extract of the posterior lobe. The physiological activity of extracts of the fresh pituitary was first investigated. Thus in 1895 Oliver and Schäfer⁴ reported the results of

their researches which demonstrated in the mammalian pituitary body an active principle with a specific effect upon the heart and bloodvessels when injected intravenously. It was shown that this extract produced a general constriction of arterioles, leading to considerable elevation of blood-pressure and an augmentation of the force of the heart beats.

Howell ⁵ subsequently pointed out that the posterior lobe alone possesses this property. Dale ⁶ was the first to describe the direct stimulating action of pituitrin (the active principle derived from the posterior lobe) on the uterine musculature. Blair-Bell ⁷ in addition described its stimulating action upon the musculature of the bladder. Frankl-Hochwart and Fröhlich ⁸ experimented further with hypophysin, a pure extract of the posterior lobe, and confirmed and elaborated the findings of Dale and Blair-Bell. The galactagogue action of posterior lobe secretion, as described by Ott and Scott ⁹ and as further investigated by Mackenzie may be mentioned in passing as bearing out the relationship of the pituitary body to milk secretion during and after pregnancy. Whether this action of posterior lobe principle is one specifically stimulating to the secreting mammary cells or whether it produces its effect by causing contraction of the smooth muscle fibers around the ducts of the gland, thus causing the expression of milk, remains an open question.

C. EFFECT OF FEEDING ANTERIOR LOBE. Many attempts have been made to simulate conditions of hyperpituitarism by feeding with fresh gland or glandular extracts over long periods of time. The primary object of these experiments was to study the effect upon the growth of the animals. The results reported vary greatly and probably to a large extent for reasons mentioned above. Practically no observations had been reported on the effect of experimental overstimulation with pituitary extracts

upon the development and activity of the sex glands until the author's publication upon the subject in February, 1916.¹⁰ Behrenroth¹¹ is the only previous author, in so far as I have been able to discover, who makes any special mention of an accompanying effect upon another of the ductless glands, produced by either the feeding or by the injection of pituitary extracts. He carried out the hypodermic administration of pituitary extract mainly for the purpose of observing its action upon the kidney, blood-pressure and metabolism. He incidentally makes brief mention of the fact that in some of his animals early and extensive spermatogenesis was noticed. The results, however, were not constant and in female animals only slight changes were observed.

In view of the definitely retarding influence upon the growth of the sex glands produced by partial extirpation of the pituitary gland, it occurred to the writer that it might be possible to produce premature sexual development and maturity and overactivity of the sex glands in young animals by the prolonged daily feeding of small doses of pituitary extract (anterior lobe) to young animals. Accordingly feeding experiments were carried out in young rats to which daily doses of .05 gm. of the dried powdered extract of the anterior pituitary lobe were given over varying lengths of time, beginning when the animals were weaned, which was usually at the age of 3½ weeks. The feeding of whole gland exerts its action by virtue of the anterior lobe extract which it contains, for it was found that the extract derived from the posterior lobe had no specific action upon the development of the sex glands.

The conclusions cited in the above study (p. 49) may be briefly repeated here.

"In comparison with the development in control animals, the ovaries, tubes, and cornua of the uterus of animals fed with whole gland extract (in which the anterior lobe is the

responsible factor) are larger, more vascular and cedematous in appearance, indicating increased development and activity. Even at the early age of $2\frac{2}{5}$ months, from one to two months before normal sexual maturity, the ovary is matured, and shows active ovulation and Graafian follicle formation, relatively few primordial follicles, and some increase in the amount of interstitial tissue. This striking appearance in so young an animal gives the impression that an early ovarian maturity has been produced by the feeding of the pituitary extract. The fimbriated end of the tube is more branched and the lining columnar cells are more ciliated, an indication of greater activity. There is marked hyperplasia of the uterine mucosa, the lining cells of which are more uniformly ciliated and active, and there is abundant gland formation in the endometrium. The appearance presented by the latter strikingly resembles in microscopic appearance the hyperplastic endometrium of early pregnancy. There is generally increased vascularity produced in the whole sexual system. The overdevelopment is apparent even in the muscle coat of the uterus, which is considerably thickened and is also more vascular. A somewhat similar change is produced by the feeding of corpus luteum to the female but not to the same degree as after anterior lobe administration."

And again the feeding of pituitary anterior lobe extract to rats over prolonged periods was studied with the following results (p. 49) "After prolonged feeding of anterior lobe extract, over a period of eight or nine months, the sexual instincts are early awakened, along with the early maturity of the sex glands. As a result of this, a pair of rats, after anterior lobe feeding over a number of months, bred earlier and oftener, the female of this pair having two pregnancies in seven months as compared with none in the female of the control pair. The effect of the anterior lobe feeding lasts throughout the adult life of the animals. The control rat never reaches the degree of development and activity shown by the animal receiving the anterior lobe extract. For even at the age of ten months, after $8\frac{1}{2}$ months of anterior lobe feeding, the latter still shows a greater, more active and mature sexual development than the control.

"The feeding of pituitary anterior lobe to parent rats exerts its stimulating influence upon the offspring in intra-

uterine life and during lactation, and, when the experiment is carried further and the feeding to the young is continued after weaning, it has an even greater stimulating effect upon growth, weight and development, and causes earlier and more frequent breeding, and an increased number of offspring in the litters. The stimulating effect upon the sex gland is greater, the longer the influence of anterior lobe administration is exerted.

"The extract of pituitary posterior lobe, even after prolonged administration, does not stimulate growth in general, nor the development of the sex glands, as does anterior lobe even after a very short period. Thus, for example, there is a much less marked development of the sex glands after administration for $2\frac{1}{2}$ months. The posterior lobe element in the whole gland extract has an undoubted retarding influence upon the development of the sex glands, an effect very similar to that of ovarian extract upon the testes. This is shown by the relatively incomplete development of the testes, for example, after $8\frac{1}{2}$ months of posterior lobe feeding. If given in too large doses, the extract causes in the rats loss of weight, a mild enteritis and increased intestinal peristalsis."

A striking illustration of the effect of pituitary feeding in the young female rat is afforded in Figs. 1 and 2. The pituitary fed animal matures prematurely and the ovary shows the presence of corpora lutea. The ovary of the control female is still immature.

In Figs. 3 and 4 the remarkable hyperplasia of the endometrium as a result of pituitary feeding is seen, a reaction so remarkable as to simulate the appearance of early pregnancy. A great increase in the number of uterine glands is also seen in the case of animals receiving gland feeding. The other changes are self-evident in the drawings.

B. CLINICAL EVIDENCE

Turning now from the experimental evidences of a close interrelationship in function between the pituitary body

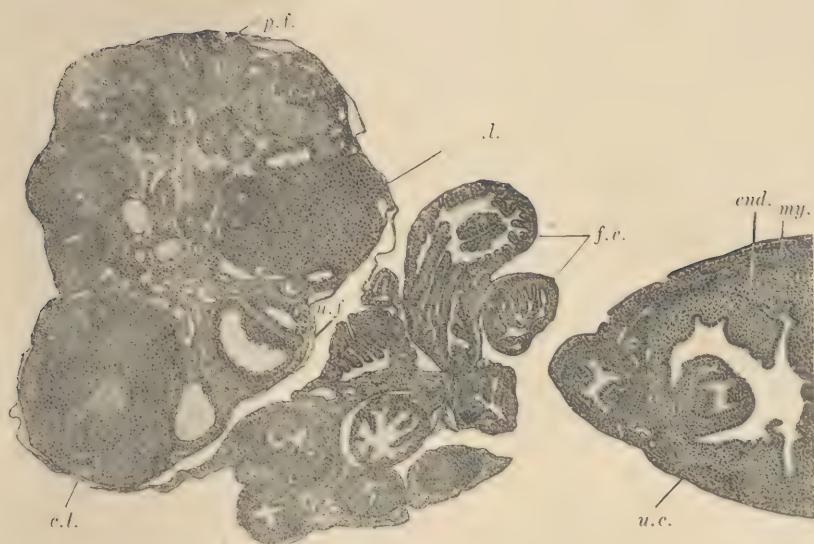


FIG. 1.—Female I (pituitary fed). $\times 18.5$.



FIG. 2.—Female II (control). $\times 18.5$.

Figs. 1 and 2 represent in one plane the ovary, the fimbriated end of the tube and the beginning of the uterine cornu of two young rats, $2\frac{2}{3}$ months old, of the same litter, to the first of which (Fig. 1, Female I, pituitary extract (whole gland) was given over a period of 42 days, from the time when the animal was 30 days old; the second, the control (Fig. 2, Female II), received no glandular feeding. Both animals were sacrificed when they were 72 days, or $2\frac{2}{3}$ months old. Compare, in Fig. 1, the presence of corpora lutea (*c. l.*), the scarcity of unripe follicles (*u. f.*), the marked endometrial hyperplasia in the uterine cornua (*u. c.*), the proliferation of the fimbriated end of the tube (*f. e.*), and the increased vascularity in the hilus of the ovary, with (in Fig. 2) the number of unripe Graafian follicles (*u. f.*); the absence of corpora lutea, the smaller degree of branching of the fimbriated end of the tube (*f. e.*), and the simple thin mucous membrane in the uterine cornu (*u. c.*). *p. f.* = primordial follicle. *End.* = Endometrium. *my.* = myometrium.



FIG. 3.—Female I (pituitary fed). $\times 24$.



FIG. 4.—Female II (control). $\times 24$.

Figs. 3 and 4 represent transverse sections through the junction points of the uterine cornua (cervix uteri) of the same rats, whose ovaries and cornua are represented in Figs. 1 and 2.

FIG. 3.—Section from the cervix of the uterus of Female I, to which pituitary extract (whole gland) was given over a period of 42 days from the time the animal was 30 days old.

FIG. 4.—Section taken from the control animal at a point corresponding to that represented in Fig. 3.

Note in the endometrium the marked hypertrophy and hyperplasia of the uterine mucosa with active gland formation suggesting the pregnancy reaction, the very cellular character of the propria, and the increased thickness of the musculature of the myometrium in Fig. 3, as compared with Fig. 4 (control). From the Bull. Johns Hopkins Hosp., 1916, xxvii, 35-36.

and the genital system to similar conditions in the human subject, bearing out this relationship, we find that these have attracted the attention of the clinician. It has been found convenient to apply to the clinical types of pituitary disease certain terms which express simultaneously our conception of the activity of the gland in these states of disordered function. In the case of the thyroid a definite symptomatology was established for conditions of overaction of the gland and called "hyperthyroidism," with exophthalmic goitre as the well-known example; similarly for conditions of underactivity of the gland, called "hypothyroidism," exemplified by myxœdema in the adult and cretinism in childhood. Just so analogous terms were chosen for states of over and underactivity of the hypophysis, namely, "hyperpituitarism" and "hypopituitarism." Practical difficulties were, however, encountered in attempting to place all types of pituitary trouble in these two groups, for conditions of presumed overactivity frequently merge into states of underactivity, so that symptoms characteristic of both states blend one with another, just as in the case of the thyroid symptoms of myxœdema are engrafted on the picture of Graves' disease. Then again, in the pituitary we are dealing with two separate lobes, either one of which may become the seat of disease without the involvement of the other, or one may become adenomatous and clinically overactive, and by pressure upon the other lobe may impair its function and cause a condition of underactivity of this part. To designate this large group of pituitary diseases the term "dyspituitarism" has been used.

In considering the symptomatology of pituitary disorders it is convenient to think of it in terms of local symptoms due to pressure by the enlarging pituitary body upon important neighboring structures and of general glandular manifestations consequent upon changes pro-

duced by excessive or deficient pituitary secretion. The change may be primarily due to the excessive secretion itself or secondarily due to consequent disorders in the other ductless glands, such as the genital glands reference to which will be made shortly.

Pressure upon parts in the immediate neighborhood of the pituitary is occasioned mostly by hyperplasia or tumor growth of the gland itself. The principal pressure symptoms thus caused may be briefly mentioned. They are headaches, usually bilateral, and due probably to distension of the dural envelope of the gland. If the tumor enlargement encroaches upon the intracranial space general headaches, frequently with vomiting, choked disc superimposed upon primary optic atrophy and disturbances due to pressure upon important neighboring cerebral areas may result. Frequently there is absorption, varying in degree, of the bony walls of the sella turcica, the study of which has been aided so much by the *x*-ray. The optic nerve is early involved, with resultant characteristic types of blindness. In the more severe grades of general intracranial pressure convolutional pressure markings on the inner surfaces of the bones of the cranial vault may be recognized by the *x*-ray.

The general glandular manifestations document themselves in changes in growth, in cutaneous and subcutaneous changes, in adiposity and alteration in the carbohydrate metabolism and tolerance, in urinary changes, in variations in body temperature, blood-pressure, in mental disturbances, and in secondary disturbances in other of the ductless glands, particularly the genital glands. Histological alterations are known to occur in the thyroid, adrenals, thymus, pancreas, and pineal, but they possibly are less definite and of less significance than those found in the genital glands and will not be considered in greater detail at the present time.

A. **HYPERPITUITARISM.** Clinical hyperpituitarism is now quite generally considered to be due to overactivity of the pituitary anterior lobe secondary to adenoma or hyperplasia of this anatomical division of the gland and evidenced histologically by a great increase in the number of eosinophile or acidophile cells. If this condition antedates puberty the resulting condition is known as gigantism; on the other hand, if the hyperpituitarism develops in the postadolescent period the well-known disease, acromegaly, develops. We are acquainted with examples of excessive sexual libido occurring in the early stages of the latter, and with cases of premature acquisition of sexual power and secondary sex characteristics if the hypophyseal overactivity antedates normal adolescence. After a period of hyperplasia and hyperactivity of the pituitary, particularly the anterior lobe, the gland undergoes a retrogressive alteration, as shown by the strumous tumor formation and the tendency to cystic degeneration of the pituitary so frequently found in the later stages of acromegaly. It is for this reason without doubt that so much confusion has arisen in interpreting the sexual changes occurring in the disease, but if we remember that the pituitary gland itself undergoes a kind of involution from a hyper-active to a hypo-active state in acromegaly, then we can readily comprehend the early increased libido and hyperactivity of sexual function and the late loss of libido and incidence even of impotence in the male and cessation of menses with sterility in the female.

In the final stage in both sexes a high degree of atrophy of the sex glands develops. Indeed it is not uncommon for the gynecologist to be the first to be consulted by the patients suffering from these pituitary disorders because of the disturbing genital changes. If it were possible to examine the sex glands in the early stages of gigantism and acromegaly one would in all probability find histo-

logical evidences of very active spermatogenesis in the male and abundant ovulation in the female. Since, however, the sex glands at autopsy are examined in almost all instances in the late stage, we find only evidence of hypoplastic change. Thus in gigantism we find skeletal overgrowth combined with genital hypoplasia and imperfectly acquired secondary sexual characteristics and in acromegaly we similarly have the well-known bony overgrowth and retrogressive sexual changes producing amenorrhea and sterility, even though the sexual functions may have been previously quite normal. Sections of the ovary analogous to those of the testis, obtained in the late stages of acromegaly show definite hypoplastic, retrogressive changes on the part of the Graafian follicles and possibly of the interstitial tissue. Corpora lutea are not present.

B. *HYPOPITUITARISM*. In primary hypopituitarism there is possibly an even more striking influence toward hypoplastic changes in the sex glands. Cases of primary pituitary atrophy or destruction by tumor formation belong in this class. If the hypopituitarism antedates puberty there results the striking condition known as "dystrophia adiposogenitalis," a condition to which Fröhlich¹² first drew attention in 1901 and which is characterized by genital aplasia, undersized stature, hypotrichosis and a characteristic adiposity, of the feminine type when it occurs in males. There is a failure of development of the secondary characters of sex, and puberty may be delayed or may not appear at all.

If a similar condition develops after puberty has been reached one would of course not expect to see such striking reversive tendencies, but we do see a marked tendency to adiposity, hypotrichosis, often subnormal temperature, slow pulse, dry skin, a high sugar tolerance, and irregularities in sex function, which express themselves in scanty irregular menstrual periods, amenorrhea and sterility. The ovaries show definite retrogressive change.

C. DYSPIUITARISM. Certain clinical cases are met with in which there is a combination of symptoms and findings of both the hyper and hypopituitary state. These are grouped under the term of "dyspituitarism."

III. PITUITARY CHANGES SECONDARY TO PRIMARY ALTERATIONS IN THE SEX GLANDS

A. IN PREGNANCY. The converse interrelationship from that just considered, that is, a pituitary change secondary to primary alteration in the sex glands, is also illustrated by clinical and experimental conditions. Thus Compte¹³ in 1898 was the first to show that there was an increase in weight of the hypophysis at the end of pregnancy, due to hyperplasia and hypertrophy of the anterior lobe. Erdheim and Stumme¹⁴ first demonstrated the pregnancy hypertrophy of the hypophysis in the human and carefully described the essential changes which occur in the anterior lobe. These changes are due to the accumulation in large numbers of a new cell type, the pregnancy cell, derived from the chromophobe or chief cell. These large pregnancy cells which are clear and neutrophilic dominate the picture, while the eosinophilic cells, markedly decreased in number, are crowded aside into the more central portions of the gland acini. The histological picture thus afforded is very striking. The hypertrophy of the pituitary occurring in the later stage of pregnancy may become so marked as to exert pressure upon the adjoining optic chiasm sufficient to cause a transient bitemporal hemianopsia, cases of which have been reported from time to time. Associated with this hypertrophy occurring in pregnancy there may be signs and symptoms attributable to a temporary hyperfunction of the pituitary, such as definite change in thickness of the nose and face and enlargement of the hands and feet. Similarly a transient

glycosuria may be found, possibly due to transient hyperfunction of this gland. Within a few months postpartum retrogressive changes occur, the pregnancy cells return to the type of chief cells and the gland once more assumes its normal appearance. The involutions of the gland may be incomplete and after repeated pregnancies there may result a kind of strumous degeneration followed by symptoms dependent upon a deficiency in pituitary secretion.

B. AFTER CASTRATION. On the other hand, in castration, both in animals and in the human, it has been shown that there is a consequent hypertrophy of the hypophysis. Fichera¹⁵ was the first to demonstrate that in a series of castrated animals of different species, including the cock, ox, buffalo, guinea-pig and rabbit, there was a definite increase in the weight of the hypophysis, relatively greatly in excess to the increased growth of the animal. Histologically, in addition to the hyperæmia there was an increased number of eosinophiles. Tandler and Grosz¹⁶ were similarly able to show an hypertrophy of the pituitary body in the castrated human, as indicated by enlargement of the sella turcica, demonstrable by the *x*-ray in the living and by examination of the skeleton after death. Tandler¹⁷ showed that a pituitary hypertrophy following castration occurred not only in the skopzen sect of eunuchs, but that the same condition occurred also in castrated women. For a more detailed account of the genital changes occurring in clinical cases of pituitary disease the reader is referred to the case reports and particularly to Part III, pp. 275-280, of Cushing's¹⁸ comprehensive monograph "The Pituitary Body and Its Disorders."

IV. THE USES OF POSTERIOR LOBE EXTRACT IN OBSTETRICS AND IN INTESTINAL PARESIS

A. IN PREGNANCY. Very soon after our understanding of the action of pituitary extracts upon the genital system

became more definite, these substances were applied therapeutically in clinical cases. Thus Herzberg²⁰ used intramuscular injection of an active pituitary product called "hypophysin," in cases of pregnancy, with apparent success in causing more powerful contraction of the uterus during parturition. Because of its characteristic stimulating action upon smooth muscle generally, and particularly and almost specifically upon the pregnant uterus, pituitary extract (posterior lobe) has come into wide use in obstetrics. The extract on the market is known as "Pituitary Liquid" or as "Pituitrin." It is a carefully prepared solution of the active principle of the posterior lobe and can be standardized by the isolated uterus method. This latter method enables us to know the exact strength of solution which we are using. Pituitary Liquid represents the active principle of the pituitary posterior lobe in normal salt solution and is put up in 1 c.c. ampoules convenient for hypodermic use. According to Fenger²¹ "The uterine contracting principle of the posterior lobe of the pituitary body is readily extracted from the fresh glands by water and also by neutral and acidulated methyl or ethyl alcohol. The acidulated methyl alcohol extract is more than twice as strong as the water extract and somewhat stronger than the pure crystalline β -imidoazolyethylamine hydrochloride." "Pituitary Liquid" is now official in the new pharmacopeia.

In an article entitled "Observations on Pituitary Extract in Obstetrics," published in May, 1915, Rowland²² reports the results of a careful study on the use of pituitary posterior lobe in a series of obstetrical cases. I shall borrow freely from this report in my consideration of this phase of our subject.

The easy administration of the drug, the very satisfactory results in properly selected cases, the apparent harmlessness of its use, the apparent saving of many cases from operative

delivery and particularly the almost immediate termination of labor after hours of tiresome waiting by the physician and the painful and exhausting labor for the patient all make a very strong appeal to the obstetrician. For this reason the dangers of pituitary administration, for there are real dangers in its use, should also be impressed upon those using this drug.

The uterine contractions, caused by hypodermic administration of the drug last from 30 minutes to about two hours or longer with an average duration of about one hour. They are increased in intensity and the intervals diminished. In cases of labor the effect of the drug is first shown in less than ten minutes after administration. The contractions experimentally induced, are in the beginning not accompanied by pain, and in cases in the second stage the great increase in strength and efficiency of contractions does not seem to be accompanied by a relative increase in the patient's suffering. Exceptions, however, do occur. The contractions are not tetanic in character though sufficiently continuous and severe in some cases to cause concern if there is obstruction or a diseased condition of the uterine wall. There is usually an increase in the blood-pressure independent of the intensity of the pains set up, with an average increase of about 18 to 24 mm. Hg. The increase is usually gradual for about 20 to 30 minutes followed by a slow return in the course of an hour to the pressure present before injection. From the standpoint of toxicity the drug seems on the whole to be harmless. There are cases however of individuals who seem to possess an idiosyncrasy toward the drug and who respond to it by having nausea and vomiting and in a few instances even collapse.

There seems no doubt now that labor can be induced by the use of pituitrin. By its use it may be possible to terminate a full term pregnancy, when it is desirable to do so. The use of pituitrin is dangerous in cases where there is failure of the cervix to dilate and when the head fails to advance and engage. Marked disproportion between the head and pelvis furnish probably the strictest contraindication to its use. In proper cases, a head which has resisted the unaided efforts of the uterus to engage it, may be quickly engaged and advanced so that a forceps delivery may be done.

Dangers however arise when the pituitrin fails to do what is desired and there arises a demand for immediate delivery, for then other valuable methods for rapid delivery are made impossible. A few cases of rupture of the uterus have been reported when the drug was used in the first stage of labor. It is useful in the first stage of cases of placenta prævia in conjunction with tampon or balloon, and in cases of pre-eclamptic toxæmia, eclampsia or nephritis when the increase in blood-pressure is not considered of itself dangerous.

It is in the second stage of labor, however, when pituitrin is most valuable. In considering its use here I can do no better than quote from Rowland's observations. "All authorities agree that the period of greatest usefulness of the pituitary preparations is during the second stage of labor. Many women are able to fully dilate the cervix but make no further progress, or may fail to engage a head in the slightly contracted pelvis, or may advance the head partially through the birth canal, or may even bulge the perineum with the advancing head or breech, and then succumb to exhaustion. For one reason or another it is the second stage which has usually brought the exhaustion, fatal to the hoped for spontaneous delivery. It is here that the remedy shows its almost magical quality, terminating sometimes in a few minutes, cases which have dragged to an almost interminable length, or quickly changing a slow and exhausting second stage with weak and far apart and insufficient pains into vigorous, forceful and efficient bearing down pains which make the patient and her friends as well as the attendant have hope of a speedy termination. No other remedy or method of delivery can bring, when successful, such a change in the outlook of what has been a tedious and wearisome case. It will make an easy low forceps sufficient, when a difficult high forceps would otherwise have been necessary. It practically does away with the cases which otherwise would terminate in a low forceps delivery."

There are certain disadvantages and dangers in the use of pituitrin which should be mentioned. It should not be given at all or administered with the greatest caution when there is obstruction or a diseased or weakened condition of the uterine wall. There is more damage to the perineum

than in corresponding cases delivered spontaneously, but the disadvantage is offset by the number of forceps deliveries from which patients are saved. There is danger of asphyxiation of the child if for any reason delivery is delayed while the placenta is being separated from the uterus. The sudden and rather prolonged rise of blood-pressure may be a complicating factor in some instances. The possibilities of rupture of the uterus have been mentioned. Certain definite advantages in addition to those mentioned above may be cited. There is less hemorrhage after delivery. Pituitrin, however, has not displaced ergot in stopping hemorrhage.

It has been claimed by some that pituitary liquid will distinguish between pregnancy and labor, the basis for the differentiation being that a small dose of the drug ($\frac{1}{3}$ c.c.) will start uterine contraction if pregnancy has reached term, but if administered before term the effect is transient and additional doses will have no effect. It seems that when thus used the drug sensitizes the pregnant uterus but does not stimulate strong contractions.

In the obstetric clinic of the Johns Hopkins Hospital, Williams is making rather extensive use of pituitary liquid. The indications for its use have been grouped under three heads.

In the first place pituitary liquid is used in primipara only when the head is beyond the spines and on the perineum thus assuring free passage to the head. In multipara it is used frequently even when the head is at the spines, no bad results having been seen in its use at this stage. The general results have been very satisfactory and as a consequence of this therapy there has been a very considerable reduction in the use of forceps.

The second use of this drug by Williams is for the arrest of hemorrhage postpartum, instead of ergot. It acts more rapidly than ergot—inside of 3 to 5 minutes—and is always followed by the latter given hypodermically. In cases of

severe hemorrhage, or in which further hemorrhage is feared, ergot may also be given by mouth. The reason for this mode of treatment lies in the fact that the effect of pituitary liquid is rather transient, the subsequent administration of ergot being intended to cause continued contraction of the uterus after the effect of the pituitary drug has worn off. For a similar reason pituitary liquid is used in cases of complete uterine atony after forceps have been applied.

The third use is in cases of Cæsarean section in which this drug is used as a prophylactic against hemorrhage. Formerly a hypodermic of 1 ampoule (1 c.c.) of the drug was given just before the beginning of the operation. This time was chosen on a basis of allowing 3 minutes for delivery, since the action of the drug is rather rapid. In cases however of inability to deliver in 3 to 5 minutes as a result of operative difficulties there is a distinct danger of asphyxiation of the child. Consequently this mode of administration was given up and a change was made in the time of injection of the drug. At present the syringe is ready, the ampoules are previously sterilized and the injection is given directly into the posterior wall of the uterus just as soon as the baby is delivered. The action of the drug is very rapid, the uterus contracts powerfully and usually becomes board-like in $1\frac{1}{2}$ to 2 minutes. This treatment has now become the routine in these cases and the results have been very satisfactory.

The pituitary liquid is not given at all in Williams' clinic in the primary stage of labor. In a few earlier instances in which the drug was given at this stage, violent pains were produced of such severity that chloroform had to be administered to the patient. No serious results however were experienced. The principal dangers that should be mentioned are rupture of the uterus when the drug is given in the first stage when the cervix is not dilated and particularly in cases of weakness of the uterine walls. The second major danger is asphyxiation of the child in those cases where rapid delivery subsequently becomes impossible. The drug acts in from 3 to 10 minutes and the effect lasts for $\frac{3}{4}$ of an hour to one hour. If it has not acted in 10 to 15 minutes it is safe to repeat the dose. Frequently it is found that $\frac{1}{2}$ c.c. is just as effective as 1 c.c. and repeated doses when indicated can be given without dangers except of course those men-

tioned. Since the action of pituitary liquid is rather transient there is still a definite use for ergot, which is used very extensively secondary to the previous treatment with pituitary liquid. The latter has also been used for the relief of distension with considerable success. For the relief of this condition the treatment is the same whether the patient is a primiparous or multiparous woman. No disagreeable after-effects from the administration of this drug have been observed such as nausea, vomiting, collapse or disturbances of the circulatory system.

B. IN INTESTINAL PARESIS. Because of its stimulating action upon the smooth musculature of the bowel pituitary liquid has been used rather extensively for intestinal paresis and distension following abdominal and pelvic operations. The dose used varies from .5 to 1.5 c.c. injected intramuscularly in the gluteal region. The first dose is usually given from four to six hours after operation and may be repeated a number of times at intervals of four to six hours, according to indications. According to the reports published no serious results seem to have followed this treatment. In many cases markedly beneficial effects have been observed, such as early passage of flatus, cessation of abdominal discomfort and a freer movement of the bowels. Catheterization seems to be less frequently necessary on account of postoperative retention of urine, since bladder irritability is also increased by injections of pituitary liquid. The injections should be given intramuscularly because the subcutaneous injections are apt to produce considerable pain and may be followed in certain instances by local necrosis.

V. THE USE OF PITUITARY EXTRACTS IN DISEASE OF THE PITUITARY GLAND

Considerable success has furthermore been attained by the oral or hypodermic administration of pituitary extracts

in clinical cases of pituitary disease exhibiting among other symptoms the characteristic sexual disturbances such as amenorrhœa and sterility in the female and the loss of libido and potentia sexualis in the male. A number of such cases have been recorded by Cushing¹⁹ in which after administration of pituitary extracts by mouth, there has been a return in part or entirely of menstruation and of libido and potentia. It seems probable that in conditions interfering with the normal function of the pituitary gland, both the anterior and posterior lobes are involved, and that we therefore see in the corresponding clinical states symptoms due to disturbances in both lobes. Reference was made in a previous section of this paper to the experimental facts which showed that a deficiency in posterior lobe secretion is followed by a tendency to the deposition of fat and to changes in metabolism, such as an increased tolerance for carbohydrates, and that these changes can be favorably influenced by the administration of posterior lobe extract. The genital disturbances, which follow deficiency in pituitary anterior lobe function and which are associated with these changes just mentioned are benefited by the administration of anterior lobe extract. It follows then that in order to obtain the greatest benefit in clinical cases which combine the symptoms of deficiency of both pituitary lobes, one should administer the whole gland extract derived from both lobes of the gland.

Since many clinical states may present symptoms often very similar and yet dependent upon a different etiology, patients may complain of disturbances in genital function dependant upon changes primarily in the sex glands or secondarily due to disturbances in pituitary function. It is of advantage in the treatment of these cases to determine, in so far as this is possible, whether the symptoms complained of are pelvic or pituitary in origin, for it seems definitely shown that better results are obtained when the

extract of the gland primarily deficient is given and perhaps supplemented by one or more extracts of the glands secondarily involved. Thus in a case presenting a symptomatology clearly pituitary in origin with secondary ovarian involvement, emphasis should be placed upon pituitary feeding supplemented by ovarian or corpus luteum administration, and in a case in which the opposite is true, the converse method of glandular feeding should be instituted. In a series of cases illustrating types of genital under-function and adiposity recently reported by Vest,²³ in which marked improvement followed the administration of ovarian and corpus luteum extracts, it is possible, as the author suggests, that even greater benefit might have been derived by the supplemental feeding of pituitary extract. This would seem to be the case particularly with reference to the adiposity which could be explained by a coincidental underfunction of the pituitary. Indeed the degree of reduction of the adiposity and the carbohydrate tolerance, which is usually high, might be used as an index to the dosage of gland extract which should be used. At times in cases exhibiting polyglandular manifestations small amounts of thyroid extract or even adrenalin may with benefit be added to the pituitary feeding. In addition to the improvement in the specific symptoms complained of there is improvement also in the associated symptoms. Thus subnormal body temperature again becomes normal, the blood-pressure rises, constipation is less troublesome and there is less drowsiness and mental inactivity. In gigantism and acromegaly it is obviously necessary to determine whether the disease is early and in the stage of pituitary overactivity, for at such a time administration of pituitary extract might well result in exacerbation of the symptoms complained of, just as the symptoms of exophthalmic goitre may be aggravated by thyroid administration.

Unfortunately in the present state of our knowledge organotherapy is largely empirical. The principal reason for this lies in the fact that thus far it is impossible to determine how much active principle is contained in a given amount of the dried gland extract such as is used so largely in the treatment of clinical cases. Certain active liquid preparations are at present prepared by the larger pharmaceutical firms, but the difficulties accompanying often repeated hypodermic injections are too obvious to need mention. The latter method of administration, however, is the most effective and the most satisfactory, if not continued over too long a period of time.

A uniform method of standardization of the extract used is very essential for successful therapy. Fortunately the feeding of pituitary extracts is unaccompanied by any special dangers such as are known to follow the administration of thyroid extract. In fact Cushing reports that in one of his cases in the late stage of acromegaly he gave as high as 100 grs. daily of whole gland pituitary extract in order to get the desired benefit. A convenient dosage to begin with is one which represents the administration by mouth of 5 grs. of actual dried extract three times a day, increasing until improvement is noticed. It should be noted here that many of the tablets, placed in the hands of the profession, contain accessory substances used in their manufacture and hence represent much less of the active gland substance than their weight might indicate.

Attention should be drawn to this point, as otherwise a patient might well receive a dose considerably smaller than is desired and intended. The amount of extract of other ductless glands and the mode of combination naturally would depend upon the indications in the case. Unfortunately this again of necessity is empirical, and one can be guided only by the effects produced. The greatest benefits derived from gland therapy are those obtained by

correct and patient administration over considerable periods of time, from three months to a year or more. Both experimental and clinical experience has shown that specific results are only obtained after a considerable lapse of time and many of the failures reported are undoubtedly due to too short duration of gland administration. Then again the dosage may be too small to produce results when an increase would be of distinct benefit. Thus with pituitary extract it often becomes necessary to increase the amount of gland until a definite therapeutic effect is shown.

VI. SUMMARY

Perhaps between no two of the ductless glands is a closer interrelationship in function demonstrable than between the pituitary and the sex glands. There is abundant evidence available at the present time for believing that such a close association in function exists. We know from experiments in which the pituitary gland has been partially removed in dogs that a deficiency in pituitary secretion thus produced is followed by underdevelopment, genital inactivity and hypoplasia in young animals, and by impotence and sterility and retrogressive changes in the sex glands, together with adiposity in case the animals were adult at the time of operation. Conversely after primary alterations in the sex glands, as is seen in pregnancy or after castration, there is a consequent hyperplasia and hypertrophy of the pituitary gland. Overstimulation of young animals with the extract of pituitary anterior lobe is followed by overdevelopment and marked increased activity of the sex glands. Even histological evidences of such increased function are apparent, such as premature sex development evidenced by early and abundant ovulation in the female. It is the secretion of the anterior lobe of the pituitary which is responsible for

these sex changes, whereas the posterior lobe secretion has an important function in regulating, certainly in part, carbohydrate metabolism, absence of this secretion being followed by a tendency to adiposity.

Clinical hyperpituitarism is well exemplified in the diseases, gigantism and acromegaly, now generally believed to be due to an overfunction of the anterior lobe of the pituitary gland consequent upon adenomatous hyperplasia. In the early stages of these diseases we find an exaggerated sexual activity and libido, and in the late stages corresponding with pituitary involution and inactivity, a disappearance of the sexual function. The sex glands in this late stage show, histologically, atrophy and various forms of degeneration. Similarly inactivity and atrophy of the sex glands, is seen in clinical cases of primary hypopituitarism, dependent upon pituitary underfunction following upon diseases of this gland or of its neighborhood compromising its function.

Pituitary extracts have gained wide usage in therapy. Thus "Pituitrin" or "Pituitary Liquid," derived from the posterior lobe (together with pars intermedia) because of its stimulating action upon the smooth musculature of the uterus and bowel is used very extensively in obstetric practice and for the relief of abdominal distension and intestinal paresis following surgical operations in the abdomen or pelvis. The results obtained by the correct usage of this drug are most satisfactory.

As a result of the facts learned from the experimental feeding of pituitary extracts, particularly of the anterior lobe we should feel encouraged in our efforts to benefit clinical states dependent upon underfunction of this gland in the human. Thus, for example, a number of clinical cases showing among other symptoms, characteristic sexual disturbances (irregular menstruation, amenorrhœa, sterility), dependent upon primary pituitary disease, have

been so greatly benefited that there have been a return of menstruation and libido even when these had been absent for a considerable period. It is probable that many clinical conditions showing genital aplasia, adiposity and under-development and dependent upon changes in one or more of the ductless glands other than the pituitary, would be benefited by the feeding of pituitary extract in addition to the extract of the gland which is primarily involved. On the other hand, the feeding of extracts, such as thyroid and adrenal, combined with pituitary in clinical cases of pituitary diseases in which symptoms referable to these glands are present is advisable.

CONCLUSIONS

1. There is a close interrelationship in function between the pituitary and sex glands, a fact supported by abundant experimental evidence and by numerous observations on pituitary disturbances in the human subject.

2. Overfunction of the pituitary anterior lobe is associated with overactivity of the sex glands.

3. Deficiency of pituitary secretion in the individual is followed by underdevelopment and genital aplasia in the young and by sexual inactivity and retrogression in the adult.

4. Primary alterations in the function of the sex glands, as in pregnancy and after castration, are followed by pituitary hypertrophy and hyperplasia.

5. The specific action of posterior lobe extract ("Pituitrin," "Pituitary Liquid") upon the smooth musculature of the uterus and bowel has led to the wide usage of this drug in obstetrical practice and in the treatment of intestinal paresis following abdominal and pelvic operations.

6. The administration of pituitary extracts is of distinct benefit in clinical states of pituitary underfunction.

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THE PINEAL GLAND

THE PINEAL GLAND'S INFLUENCE UPON GROWTH AND DIFFERENTIATION WITH PARTICULAR REFERENCE TO ITS INFLUENCE UPON PRENATAL DEVELOPMENT

BY CAREY PRATT McCORD, M.D.
Detroit, Mich.

I. INTRODUCTION

(A cursory review of recent work pertinent to pineal functioning.)

THE evidences that link the pineal body with a glandular function are much less definite than for such glandular organs as the thyroid, hypophysis, ovary, and the suprarenals. Doubt is frequently expressed that the pineal body is more than a functionless vestige of what was once, in earlier evolutionary stages, a functioning eye. Other observations have led to the contention that the pineal, through metamorphosis, has become a highly specialized tissue that serves the body in a manner comparable with the major members of the endocrinous system.

The purpose of the present paper is to group the essential findings from the recent literature into a concise, unbiased résumé, adequately expressing the status of the pineal body as a functioning organ. To this are added the writer's more recent observations upon the growth of young animals under the influence of pineal materials.

ANATOMY AND EMBRYOLOGY

(Bibliography numbers 1-57)

The pineal body (pineal gland, epiphysis, conarium) is situated in the brain just beneath the splenium of the corpus callosum. (Fig. 1.) It lies suspended between the anterior quadrigeminate bodies. The gland is consequently just above the Sylvian aqueduct. The internal cerebral veins lie above and partially encircle the pineal. In the human the pineal is nearly trilateral in shape, in sheep is round, in cattle is oval. The average weight in cattle is .2 grams and in sheep .13 grams. Primarily the pineal is developed as a thin endymal diverticulum from the diencephalon, extending between the posterior and habenular commissures. At a later stage this diverticulum thickens and encloses some of the adjacent vascular mesoderm to form the mature organ. (Streeter.)

In those publications cited in the bibliography as pertinent to the anatomy, embryology, and histology of the pineal, the studies have, for the most part, been prosecuted toward establishing (1) the presence of glandular tissue; (2) the presence of contractile tissue supporting the view that the gland is a valve regulating the flow of cerebrospinal fluid; (3) nerve fiber communication between this gland and other parts of the brain; (4) evidence of involution changes in the gland indicating a cessation of function.

These publications may be summarized as indicating: (1) Complete cytologic studies in several species allow the inference that the pineal body is glandular in nature. The glandular elements, however, are few and illy defined. (2) The occasionally demonstrated muscle fibers in the pineal are without significance to pineal function. (3) Nerve fibers and neuroglia are to be found at least in certain animals, but these are probably of trivial import.

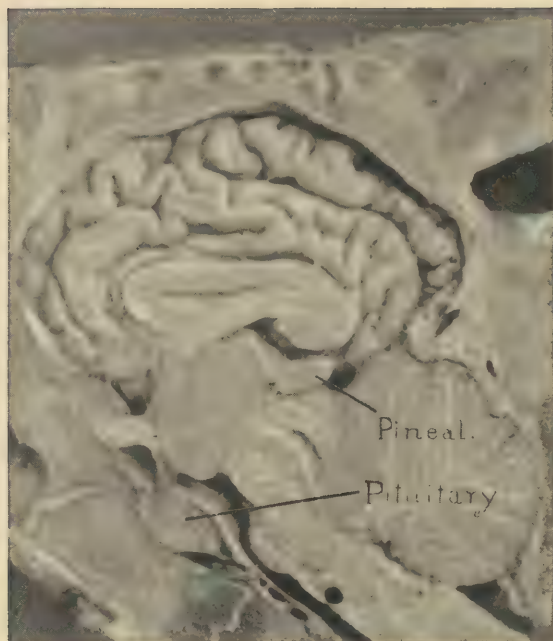


FIG. 1.—Sagittal section of beef brain, showing size, position, and relation of pineal gland.

(4) The gland undergoes involution changes, beginning in the human as early as the seventh year. Involution is pronounced at puberty. The degeneration is, however, not complete and the histologic picture of the adult gland is not such as to remove the possibility of a continued function in adult life.

PINEAL NEOPLASMS AND RESULTING FUNCTIONAL
DISTURBANCES

(Bibliography numbers 100-189)

Tumors of the pineal are not of frequent occurrence. The total number of authentic cases, with subsequent necropsy findings in some, is not more than 70. These cases have been the source of the greatest information as to the functions of the pineal. In 1898, Heubner described a boy of 4½ years who showed a precocious sexual and somatic growth. The body of this boy was that of a boy of 8 or 9 years. The genitalia corresponded to the proportions found at puberty. The pubic hair was 1 cm. long. A year later at autopsy a teratoma of the pineal was demonstrated. By 1907, Marburg was able to collect 40 histories of such types. He sought to establish a clinical entity for pineal dysfunction. The term "Macrogenitosomia præcox" has subsequently designated this condition. In a more recent paper, Marburg attributes to the condition the following characteristics:

1. General. These include all the usual signs of intracranial pressure, usually secondary to a subsequent internal hydrocephalus.

2. Neighborhood. These for the most part are dependent upon encroachment upon the quadrigeminate bodies, leading to diverse oculomotor paralyses and pupillary disturbances, and encroachment upon the cerebellum, with ataxic manifestations.

3. Constitutional. Under this designation are grouped the manifestations attributable to the derangement of the pineal glandular function. This constitutional syndrome consists of first, early sexual maturity, evidenced in the enlarged sex organs, pubic hair, general body hair, early change in voice; second, precocious mental development, evidenced in the maturity of thought and speech; third, general body overgrowth to the extent that a child of 5 or 6 years may have the appearance of a child of 11 or 12.

Frankl-Hochwart similarly has summed up the characteristics of this pathologic state. He states, "When one finds in a very young individual, along with the general symptoms of tumor as well as the signs of a lesion of the corpora quadrigemina, abnormal body growth, unusual growth of hair, adiposity, somnolence, premature genital and sexual development, and finally intellectual maturity, one must think of pineal tumor."

Of the 70 cases at the present time available in the literature, only 25 occurred prior to puberty. Because of the pineal involution that occurs by the time of puberty, only in these 25 cases are constitutional manifestations to be anticipated. It is significant that with two exceptions all cases occurred in boys.

Many cases of pineal tumors before puberty manifest none of the signs of precocity of development that are so striking in a few selected cases. A study of the clinical material reveals how little consideration has been given to the possibility of pluriglandular involvement. In fact, in some early cases the necropsy demonstration of a pineal tumor led to the association of all prior metabolic changes to pineal functional perversion. This grew out of the prevalent conception of each endocrine gland as an entity entering into no interrelations with other similar organs. Judging these cases in the light of recent advances in pituitary pathology and physiology, it is difficult to delineate

the manifestations of pure pineal derangement from a pluriglandular condition. Cushing has pointed out that from the intracranial alterations attending pineal neoplasms, the hypophyseal functions are readily deflected from the normal.

This infrequent condition in which growth and differentiation into the adult is so deviated from the normal that very young children acquire in part the sexual, mental and somatic characteristics of maturity, has naturally led to diverse attempts to induce such a condition experimentally. Through the extirpation of the pineal, through the feeding of pineal substances to young animals, through the intravenous and subcutaneous administrations of pineal extracts, has information been sought as to the significance of this organ in the body's economy. The outcome of such investigations are described in subsequent paragraphs.

EXTIRPATION OF THE PINEAL GLAND

(Bibliography numbers 71-78)

Situated near the center of the brain, the inaccessibility of the pineal has prevented any widespread use of this method. The trauma is necessarily severe and until the recent reports by Dandy (1915) and Horrax (1916) the mortality has been very high—75 deaths out of 95 operations in one series, and 12 deaths out of 15 operations in another. With so high a mortality it may be questioned whether the few survivors would exhibit constant changes referable to pineal deprivation. The mortality is usually due to hemorrhage into the ventricle from injury to the central cerebral veins, or to direct injury to the quadrigeminate bodies or adjacent brain tissues. Dandy has recently developed an operative procedure whereby much of the trauma is obviated. The essential innovation lies in

an approach through section of the splenium of the corpus callosum, thus permitting freer manipulations in the operating field. Although the mortality may thus be reduced, the results obtained by Dandy, on comparison with those obtained more recently by Horrax, are uniformly dissimilar. The respective summaries of these two investigators quoted below indicate how incomplete are our available data bearing upon extirpation as a method of approach to the problems of pineal function. Dandy states:

"1. Following the removal of the pineal I have observed no sexual precocity or indolence, no adiposity or emaciation, no somatic or mental precocity or retardation.

"2. Our experiments seem to yield nothing to sustain the view that the pineal gland has any active endocrine function of importance either in the very young or adult dogs.

"3. The pineal is apparently not essential to life and seems to have no influence upon the animal's well being."

These negative findings are in keeping with the earlier work of Exner and Boese, and Biedl. Subsequent to Dandy's publication an extended report has been made by Horrax, whose positive findings are in keeping with those of Foa and Sarteschi. Horrax states:

"1. Total experimental pinealectomy is possible in guinea-pigs and rats.

"2. Pinealectomized male guinea-pigs show a hastened development of the sexual organs, manifested before maturity by a relative increase in size and weight, both of the testes and seminal vesicles, over control pigs of the same litter.

"3. Histologically the testes and seminal vesicles of these animals, if taken before the age of sexual maturity, show a more advanced physiological state than their controls.

"4. The pinealectomized females appear to show a tendency to breed earlier than controls of the same age and weight.

"5. For several reasons, young rats are likely to prove better subjects for experimental pinealectomy than young guinea-pigs, and some evidence of hastened maturity has been obtained in this species."

IMMEDIATE RESULTS FOLLOWING THE INTRAVENOUS OR SUBCUTANEOUS ADMINISTRATION OF PINEAL EXTRACTS

(Bibliography numbers 58-70)

Unlike the intense cardio-vascular action of suprarenal extracts, or the uterine contracting action of pituitary extracts, the immediate results from intravenous or hypo-

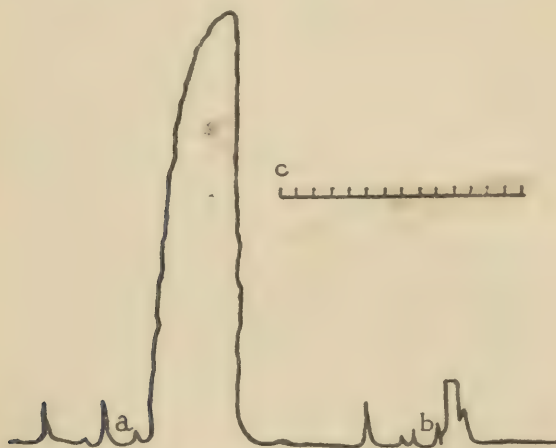


FIG. 2.—A comparison of the effect on surviving guinea-pig uterus of pituitary and pineal-gland extracts. The height of contraction from the pineal extract administered at *B* is trivial in comparison with the contraction at *A* induced by the much smaller quantity of pituitary extract. Time in minutes.

dermic injections of pineal extracts are not pronounced. Such phenomena as decrease in arterial tension, dilatation of the bloodvessels, altered amplitude and rate of the heart beat, diuresis, glycosuria, and uterine contractions have

been reported and confirmed. Under experimental conditions the contraction produced in the uterus by 1 c.c. of 20 per cent. pineal extract is much less intense than the contraction produced by 1/200 c.c. of 20 per cent. pituitary extract. (Fig. 2.) The intensity of these several activities is so slight that at the present time only technical importance may be attached to these findings.

FEEDING EXPERIMENTS WITH PINEAL GLANDS

(Bibliography numbers 79-87)

The syndrome of precocious development seen in the human is usually interpreted as the outgrowth of pineal deficiency—a hypopinealism. Such being the case, if the feeding of pineal materials determined any changes, a state just opposite that cited above would be anticipated—a condition of deferred sexual, mental and somatic maturity. Curious to record, feeding experiments lead to rapid sexual and somatic development.

Dana and Berkeley fed pineal materials to young animals (kittens, rabbits, guinea-pigs), and noted a 25 per cent. excess in weight over controls. These investigators sought to determine the extent of stimulating influence upon children of low mentality. Fifty feeble minded children were treated and suitably controlled with other children of the same age and diagnosis. Binet tests were the criteria of mental advancement. No physical changes resulted but on prolonged treatment the mental development was greater than that prior to treatment and in excess of control children of the same mental age. These studies on feeble minded children afford certain technical evidences of value but the quantity of improvement resulting is not sufficient to warrant any widespread use of pineal materials as a profitable treatment of feeble mindedness.

Hoskins (1916) in feeding experiments upon albino rats, studied the influence upon the growth of the various ductless glands including thyroid, thymus, hypophysis, and pineal.



FIG. 3.—Results of feeding pineal gland to young guinea-pigs of the same age. Animals to left, controls. Animals to right, pineal fed.

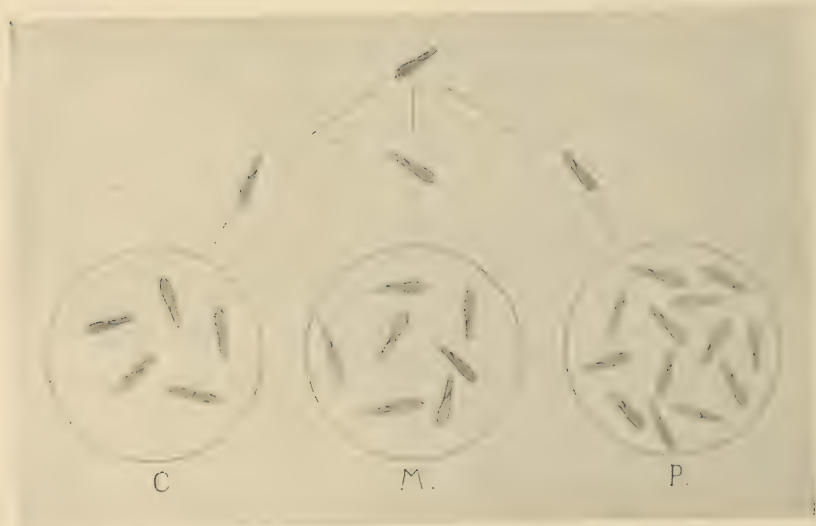


FIG. 4.—A diagram showing the modified division rates of paramecia (starting with a single paramecium). *P*, 0.05 per cent. pineal extract in hay infusion. *M*, 0.05 per cent. muscle extract in hay infusion. *C*, hay infusion alone. Diagram represents the average of thirty-six observations.



FIG. 5.—A comparison of two groups of toad tadpoles taken from the same lot, photographed simultaneously after two weeks of laboratory feeding. Group to the right fed small amounts of desiccated pineal gland triweekly. Group to the left fed equivalent amounts of desiccated muscle tissue.



FIG. 6.—Drawings made at weekly intervals indicating the rate of metamorphosis of *Bufo Americana* tadpoles fed pineal tissue in comparison with normal metamorphosis. *a* to *e* inclusive, controls. *f* to *j*, pineal fed. The small figures to the right of *a*, *b*, *f*, and *g* represent stages in the development of the hind legs for these respective tadpoles.

His results would indicate that none of these glands have any constant effect upon the growth-rate of young rats.

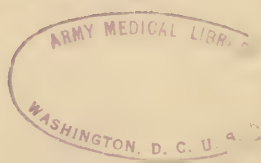
McCord (1914, 1915) employed 400 young animals (chickens, guinea-pigs, dogs) in experiments to establish the extent of influence the pineal exerts upon growth and development. He concludes from his experiments that the same precocity of development usually attributed to pineal deficiency (hypopinealism) was obtained in animals by supplying an increased amount of pineal substance by feeding or injecting pineal preparations. Such administration of pineal substances led to a more rapid growth of body than normal, and determined an early sexual maturity. The excess in rate of growth was most pronounced (40.9 per cent. excess in eleven weeks) in young animals fed with pineal tissue obtained from young animals. No tendency to gigantism has followed pineal administration. After maximum size was attained, pineal administration appeared to be ineffective. Both males and females respond to the influence of pineal substances in rate of growth, but the response has been more definitely manifested in males.

II. THE PINEAL GLAND'S INFLUENCE UPON GROWTH AND DIFFERENTIATION

(A record of experiments upon postnatal and embryonic growth-differentiation processes)

In the developmental processes inaugurated at conception two distinct phases are to be observed—growth and differentiation. In intra-uterine life differentiation into specific organs and tissues is the essential process. In pre-adult life, growth processes are dominant. At puberty differentiation again asserts its influence. In adult years both these developmental processes are less in evidence, a condition we commonly designate as maturity.

These two phases of development are necessarily intricately interrelated, but within certain limitations may be separately altered. Traces of thyroid tissue added to the water in which tadpoles live will bring about the complete



transformation of the tadpole into a miniature frog within one week, whereas normally this metamorphosis consumes from 4 to 6 months. (Gudernatch.) This phenomenon is due to the intense differentiative action of the thyroid. Similarly thymus tissue retards differentiation of tadpoles. At the period of development wherein normally tadpoles begin to differentiate, thymus fed tadpoles continue to grow larger without differentiation. Manifestly both these factors in development are ultimately dependent upon the quantity or quality of cell activity.

In our earlier records of the influence exerted by the pineal upon development we employed young animals and chicks. Variations were introduced to reduce the possibility of incidental error in dosage, in method of administration, in source of materials, in age of the test animals. With the exception of two series we have uniformly found that young animals who had been fed (or injected) pineal materials have outgrown their controls of the same age. (Fig. 3.) In one series the difference was 40 per cent. at 11 weeks of age. No tendency to gigantism was observed. As the normal adult size was approached the stimulative action of the pineal was no longer effective. The testes of certain of these rapidly developed guinea-pigs were examined in comparison with controls. Grossly the testes from pineal fed animals were 50 per cent. larger. Microscopically the cellular elements were far in advance of controls and were characterized by very active spermatogenesis. The females gave birth to young when the controls were in the middle third of their gestation. At first it was thought this might be evidence of a shortened gestation period, but more carefully scrutinized experiments determined that this was the outcome of earlier breeding, due to an earlier maturity.

At all times this type of feeding experiment is open to the error that normally such animals exhibit very appre-

cial individual variations. We have anticipated that less complex life forms that show scant individual variations even in large numbers would afford acceptable data as to any action that pineal extracts might have on their growth-differentiation processes. For the purpose, we selected (1) paramœcia (*paramœcium caudatum*), a unicellular organism that through transverse fission may divide into many generations in a single day, (2) tadpoles of frogs and toads. This larval form of the frog and toad corresponds in many respects to embryonic, intra-uterine life in higher animal life.

PARAMECIUM EXPERIMENTS

Cultures were maintained in the laboratory, growing on hay infusions. These organisms are about $\frac{1}{4}$ mm. in length and may be readily counted with the naked eye. Through transverse splitting reproduction is accomplished. Under standardized conditions the rate of divisions is relatively constant. It will be argued that in the event of constant exceptional variations in the number of generations formed when pineal materials were added to the culture medium and not occurring when other similar protein materials were introduced, that the phenomenon is attributable to pineal activity. The following procedures were employed. A single paramœcium was isolated until the reproduction of the third generation. These resulting four individuals were separated and placed in different media, (a) one in hay infusion, (b) one in a hay infusion extract of desiccated pineal gland, .05 per cent. strength, (c) one in a hay infusion extract of desiccated muscle of equal strength as a control material, (d) the fourth one was a variable control. These cultures were maintained in a moist chamber for a fixed period (48 or 24 hours). At the expiration of that time the several cultures were examined as to the numbers of reproductions. Almost invariably the divisions were more numerous in the pineal culture. For example, in one 48-hour experiment 12 individuals resulted from the plain hay infusion, 30 individuals from the hay infusion pineal extract .05 per cent. and 10

individuals from the hay infusion muscle extract .05 per cent. The results from 31 consecutive experiments are grouped in table 1.

TABLE 1. RECORDS OF DIVISIONS OF PARAMÆCIA

48-hour group				24-hour group			
No. of Expe'm't.	Hay Infusion.	Pineal Gland.	Muscle Tissue.	No. of Expe'm't.	Hay Infusion.	Pineal Gland.	Muscle Tissue.
1	7	23	..	18	7	13	..
2	7	31	..	19	3	6	..
3	11	12	..	20	11	19	..
4	5	8	..	21	3	5	2
5	1	16	..	22	4	8	8
6	1	13	..	23	6	16	4
7	4	12	..	24	4	8	5
8	5	19	12	25	10	17	10
9	5	12	9	26	11	19	..
10	13	12	4	27	4	7	5
11	2	9	4	28	1	4	3
12	2	7	6	29	1	7	2
13	3	19	16	30	3	8	2
14	1	21	12	31	5	15	5
15	10	25	23				
16	12	30	10				
17	13	22	11				
—	—	—	—	—	—	—	—
Average	6.0	17.1	10.7		5.0	10.5	4.6

The inference is, that pineal materials, when added to the culture medium of the unicellular organism, paramœcium, determines a more rapid rate of reproduction. (Fig. 4.)

TADPOLE EXPERIMENTS

The time of appearance of the successive stages in the differentiation of tadpoles into frogs is an excellent criterion of the influence of any variation in the living conditions of these animals. For the individuals of a single laying, fairly constant is the occurrence of such stages as the budding of the hind legs with the subsequent formation of the different portions of the hind legs, the closing of the gills, the extrusion of the fore legs, the assumption of terrestrial life. Such are the phenomena we sought to influence by the introduction of pineal gland materials into the living water of the tadpoles.

About 50,000 frog eggs were procured and hatched in the laboratory. These were divided into colonies of about 200 each. In most cases these colonies were from the same laying. With so abundant materials it was possible to introduce wide variations in test materials and controls. The pineal glands were fractionated into various components and tested against controls such as other endocrine glands, split proteins, histamine, lipoids, etc. Through photography and actual measurements the variations were recorded.

The present paper can make but most casual reference to the accumulated results. The photograph and drawings will serve to indicate the trend of results. (Fig. 5.) (Type photograph—adjacent trays of pineal fed and muscle fed tadpoles of the same laying.) At this stage the pineal fed, while about double the size of the controls, show no tendency to differentiation. Ultimately, however, differentiation is earlier, as may be observed in the drawings of Fig. 6.

It is our belief that the pineal gland contains some substance capable of stimulating growth and ultimately differentiation in these larval forms.

GENERAL SUMMARY

From the lack of unanimity in the literature any conclusions as to the details of pineal gland function must be made flexible rather than dogmatic. A survey of available data leads to the following summary as representing the present status of the pineal as an organ of internal secretion.

1. A clinical syndrome is to be associated with disturbances of the functions of the pineal gland. Because of the involution of the pineal at puberty, the constitutional manifestations of pineal pathology appear to be confined to prepuberal years. The essential characteristics (apart from pressure and neighborhood manifestations) are (a)

early sexual development evidenced in the enlarged genitalia, pubic hair, general body hair, early change in voice; (b) precocious mental development, manifested in maturity of thought and speech; (c) general overgrowth of body to the extent that a child of 6 or 7 years may have the appearance of a child near puberty.

2. The experimental extirpation of the pineal gland is surgically possible. The gland is not essential for the maintenance of life. The early symptoms following pinealectomy are attributable to the severe brain injury. No changes attend the removal of the gland in adult animals. As to the effects of pinealectomy in young animals, Sarteschi, Foa, and Horrax respectively state that the removal of the gland leads to precocity of development. Exner and Boese, and Dandy report no changes after pinealectomy.

3. The administration of pineal substance to young mammals is reported to hasten growth and sexual maturity. In unicellular organisms (paramœcia) pineal extracts increase the rate of reproduction to more than double that of controls. In larval forms (ranidæ) both growth and differentiation are hastened as a result of pineal feeding.

4. The inference is allowable that the pineal gland is an organ of internal secretion whose functions, however, are of minor significance in the general activities of the endocrinous system.

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THE PHYSIOLOGICAL AND PATHOLOGICAL IMPORTANCE OF THE PARATHYROID GLAND FROM THE EXPERIMENTAL ASPECT

BY CARL VOEGTLIN, PH. D.
Washington, D. C.

OUR present knowledge of the parathyroid gland can be traced back to the early studies of the physiologist, Schiff, who, on extirpating the thyroids of dogs, observed in some cases the clinical symptoms known as tetany. Schiff, however, did not associate these symptoms with the absence of the parathyroid gland in his animals as the existence of these glands was unknown in his time. The year 1880 marks the beginning of the rational study of the parathyroid gland, as in this year Sandström discovered the gland and sometime later Gley attributed to it a separate function from that of the thyroid.

In spite of the fact that the anatomy and histology of the parathyroid differ in many respects from that of the thyroid, some investigators still continued to consider these two glands to be intimately related to each other. As a result of the splendid researches of Gley, Vassale and Generali, Erdheim, MacCallum and many others, it is now generally accepted that the thyroid and parathyroid are glands with distinct and separate functions. Thus it was shown that the complete extirpation of the thyroid alone leads to hypothyroidism with typical manifestations such

as occur in myxedema and cretinism. In contrast to these observations, it was found that the complete removal of the parathyroids alone leads within a few days to the appearance of tetany. The clinical pictures of these two conditions, *i. e.*, hypothyroidism and tetany, differ so much from each other that one is forced to believe that the two glands possess separate functions. Whereas removal of the thyroid leads to a chronic disturbance of metabolism which is not necessarily fatal, the complete absence of the parathyroid is always followed by the death of the animal. The vital importance of the normal functions of the parathyroid gland for the higher animals is, therefore, self-evident.

Unfortunately our information of the physiological function of this gland is still inadequate. The only method so far available to study this problem has been the experimental production of tetany or hypoparathyroidism. By these means it is at least possible to study the changes occurring in the animal body as a result of the absence of the parathyroid gland. The most suitable laboratory animals for this purpose are dogs, albino rats and cats. With some experience all of the parathyroids can be extirpated from these animals with very little injury to the thyroid. Recovery from the operation is usually very rapid and the animal is of normal appearance a few hours later. Within a few days, however, the animal develops a state of hyperexcitability, characterized by muscular twitchings involving the skeletal muscles of part or of the whole body, fibrillation of the tongue, tachycardia, tachypnea, hyperexcitability of the peripheral nerves to the galvanic current, and increased reaction to the drugs stimulating the sympathetic nervous system. This period of hyperexcitability is usually followed by a state of depression. The animal is very quiet and refuses food. The periods of hyperexcitability and that of depression are obviously due to quite

different conditions and although the hyperexcitability is more evident, the fact should not be forgotten that the depression may be a manifestation of hypoparathyroidism. The state of depression may later on be followed periodically by hyperexcitability, a fact which may have a definite underlying cause in the metabolic changes occurring after parathyroidectomy.

NATURE AND CAUSE OF PARATHYROID TETANY

Tetany has been regarded by many authors as an intoxication by metabolic products. That the metabolism of parathyroidectomized animals is, in many respects, abnormal will be discussed later. The question which concerns us here is whether tetany is a true intoxication, in the sense that abnormal and toxic metabolic products are present in the body, or whether tetany is primarily due to an accumulation or overproduction of metabolic substances normally formed. Both conceptions are reasonable and do not stand in flat contradiction to the experimental facts.

It would probably be best to present here briefly the facts so far discovered having a bearing on the cause of tetany. This will be preceded by a short description of the symptoms of tetany as they appear after complete parathyroidectomy in experimental animals.

On carefully exposing the thyroid lobes of a dog one notices several small bodies adhering more or less firmly to the thyroid. These bodies represent the parathyroid glands and can be removed, causing little damage to the thyroid. A few days after the operation twitchings are noticed in the skeletal muscles and also in the tongue of the animal. These symptoms gradually increase in severity to such an extent that the animal is forced to lie on its side with its legs stretched out on account of spasticity. Extreme tachycardia and tachypnea are common symp-

toms at this stage of the disease. There is usually a rise in body temperature during active tetany. The attack may pass over after having lasted for several hours and the animal is then usually in a condition of depression, taking no interest in its surroundings. After a day or two the symptoms of hyperexcitability may reappear and this be followed again by depression. Death takes place during an attack of hyperexcitability or more often during the stage of depression.

The peripheral nerves during tetany show a marked increase in irritability to the galvanic current. Falta and Kahn believe that the sympathetic and parasympathetic systems also are in a state of hyperexcitability as evidenced by the increased reaction by this system to certain drugs (epinephrine, pilocarpine). It should be emphasized that increased nervous irritability is not only associated with the visible muscular twitchings but is constantly present, although to a lesser extent, even in periods of depression. This abnormal condition of the nervous system is probably not limited to the peripheral nerves but is characteristic of all nervous tissues in tetany, a fact which might find its explanation in a definite abnormality of the body fluids in this condition.

These considerations have led to attempts to control tetany by means of the administration of normal body constituents.

The work of Loeb, Sabbatani and others has shown that salts of bivalent metals with few exceptions (barium) have a depressing action on the nervous system. It was, therefore, reasonable to test the action of these salts on animals in tetany. The results obtained by MacCallum and Voegtlin, Parhon and Urechi and many others, demonstrate that an intravenous injection of any soluble calcium salt (chloride or lactate) almost instantly removes the visible symptoms of tetany as well as the abnormal irritability of the peripheral nerves to the galvanic current. Strontium salts were shown

to have an identical action as that of calcium salts. Magnesium salts also removed tetanic manifestations but the powerful depressing effect of these salts made it evident that they were not so well suited for the suppression of tetany. Moreover it was observed that similar amounts of sodium chloride or bicarbonate, potassium chloride and ammonium chloride, had no curative action; on the contrary sodium bicarbonate seemed rather to aggravate the symptoms. Later Joseph and Meltzer found that an intravenous injection of hypertonic (10 per cent.) Na Cl solution had a beneficial effect on tetany dogs. Obviously the action of the hypertonic salt solution was not due to the Na Cl per se but rather to the high osmotic pressure of the solution, an explanation which is furthermore supported by the observation that hypertonic solutions of glucose also slowly relieve the muscular twitchings. Recently Wilson, Stearns and Janney reported that an intravenous injection of dilute hydrochloric acid has the same effect on the tetany dogs as an injection of calcium. The observations of MacCallum and Voegtlin on the aggravating effect of Na_2CO_3 are confirmed and extended. Hence it is evident that a number of inorganic salts (Ca, Sr, Mg) and hydrochloric acid all possess the property of temporarily curing tetany. None of these agents, however, is capable of saving the life of parathyroidectomized animals, although animals treated in this manner may survive untreated controls.

MacCallum and Voegtlin on the basis of their results formulated the hypothesis that the parathyroid controls in some way calcium metabolism, that after the removal of this gland the body fluids and soft tissues are deprived of soluble calcium, hence the appearance of the abnormal irritability of the nervous system with all the typical symptoms of tetany. This hypothesis seems especially reasonable, if considered in connection with the splendid researches of Erdheim, who was able to demonstrate that parathyroid insufficiency is accompanied by a lack of calcification of the teeth of rats. Temporary insufficiency of the parathyroid became noticeable in the teeth of rats in

the form of a zone of deficient calcification of the dentin, preceded and followed by a normal layer of dentin. MacCallum and Voegtlin also were able to demonstrate a loss of calcium salts in the urine and feces of parathyroidectomized animals. The blood and brain calcium was also found to be reduced below normal. Later work by MacCallum, Lambert and Vogel yielded additional proof to the calcium deficiency theory of tetany. It was shown that if calcium free blood is perfused through the leg of a normal dog the irritability of the nerves supplying the leg increases markedly. Blood obtained from a dog in tetany has the same effect; on the other hand normal blood perfused through the leg of a tetany dog brings back to normal the abnormal irritability of the peripheral nerves. The injection into animals of substances such as oxalates which precipitate calcium from its solution, causes fibrillary twitchings and various other signs of hyperexcitability; this also speaks in favor of the calcium deficiency theory.

The fact that HCl is as efficient as calcium in the treatment of experimental tetany would seem at first consideration to contradict the whole hypothesis. It should be remembered, however, that hydrochloric acid is a solvent for certain insoluble calcium compounds. Furthermore it has been shown that the calcium of the blood is partly combined with proteins and other colloids and would under these conditions not be fully available to exert all its physiological actions. One might easily conceive that the introduction of hydrochloric acid directly into the blood would increase temporarily at least the hydrogen-ion concentration of the blood and in this way dissociate complex calcium compounds. The calcium set free would then become available for needy tissues such as the nervous system in tetany. In other words the treatment with acid might result in a liberation of soluble calcium from some parts of the body followed by its redistribution.

This conception would, however, obviously not be satisfactory to explain the beneficial effect of hypertonic solutions of sodium chloride and glucose. In this case the proper explanation might be as follows: Hypertonic solutions of Na Cl and glucose are known to depress the activity of certain tissues. Recently I myself observed the marked depressing effect of hypertonic Na Cl on the tonus of the smooth muscle of the uterus. Drying out of nerves is known to decrease their irritability. The injection of hypertonic solutions in tetany might, therefore, produce the disappearance of the symptoms by withdrawing by osmosis water from the tissues. Thus a considerable amount of tissue water is lost after an injection of hypertonic salt solution into tetany dogs. A marked diuresis sets in immediately after the injection is completed.

On the basis of these considerations it would seem fairly well established that calcium is intimately connected with the etiology of parathyroid tetany.

It is, however, difficult to explain why the continued administration of calcium salts does not save the life of parathyroidectomized animals. In this connection I should like to call attention to the possibility that after all tetany may represent but a symptom complex which may be very well controlled by calcium salts but is not necessarily the entire expression of the abnormality of the body following parathyroidectomy. Tetany is so to speak only one part of this pathological condition. It is highly probable that in the absence of the parathyroid, the metabolism of the body and the properties of the cells are more or less altered.

Thus Wilson, Stearns, Thurlow and Janney have recently discovered that complete parathyroidectomy in dogs is very soon followed by an alkalosis of the blood. The blood becomes more alkaline and the kidney excretes less acids and ammonia. With the development of tetany, however, the

elimination of acids and ammonia increases, this being accompanied by an acidosis of the blood and an increased hydrogen-ion concentration of the urine. Evidently some of the biochemical properties of the blood and probably also of the tissues are different during the periods of muscular hyperactivity and during the period of depression. The obvious difference in the behavior of the animal in the stage of active tetany (muscular twitchings, tachycardia, etc.) from that of depression following the active stage, therefore, finds also an expression in the biochemical composition of the blood; the first stage being characterized by an alkalosis, the latter representing an acidosis. The slight increase in the hydroxyl-ion concentration in the blood after parathyroidectomy might possibly be one of the factors concerned in the withdrawal of soluble calcium salts from the blood, inasmuch as an increase of hydroxyl-ions would tend to precipitate soluble calcium salts. On the other hand one might look upon the increased muscular activity during an attack of tetany as causing an increased production of acid products (lactic acid*) with the result of increasing the hydrogen-ion concentration of the blood which in turn might lead to a mobilization of more or less insoluble calcium compounds contained in the blood and tissues. Viewed in this light, the temporary recovery from an attack of tetany which is such a common observation in experimental tetany, might perhaps find its explanation.

The metabolism in tetany is also abnormal in other respects. Greenwald calls particular attention to the reduction in the excretion of urinary phosphates and their retention in the blood. Koch notes the excretion of methylguanidine, choline, and beta-iminazolyethylamine in the urine during tetany. This last mentioned substance was suggested by Biedl as possibly representing the hypothetical tetany poison, an assumption which seems to the author to be rather doubtful. These toxic bases are normal metabolism products and a slight increase in their excre-

* MacCallum and Voegtlin observed the presence of lactic acid in the blood of dogs in tetany and Cooke demonstrated the presence of this substance in the urine of such animals.

tion with the urine during tetany might be due to the over-activity of the muscles in this condition. Lactic acid also appears during tetany in the blood and urine and the urinary creatine is increased. These substances are known to be intimately connected with muscular activity. Furthermore, the toxic symptoms of these bases differ in many respects from those characteristic of tetany.

The accompanying table includes in a summary way the various metabolic changes following parathyroidectomy:

METABOLIC CHANGES FOLLOWING PARATHYROIDECTOMY IN DOGS

	<i>Pretetany Stage</i>	<i>Active Tetany</i>
Total nitrogen metabolism.....	Normal	Increased
Urinary ammonia.....	"	"
Blood ammonia.....	"	"
Urinary creatinine.....	"	"
Urinary creatine.....	"	"
Urinary phosphates.....	Decreased	"
Blood phosphorus.....	"	
Urinary sulphates and neutral sulphur.....	Normal	Increased
Urinary rest nitrogen.....	"	"
Urinary toxic bases.....		Present
Urinary lactic acid.....	Absent	"
Blood lactic acid.....	"	"
Urinary Ca and Mg.....	Increased	Increased
Blood calcium.....		Decreased

In summing up our present knowledge of the nature of tetany, the calcium deficiency hypothesis first advanced by MacCallum and Voegtlin still seems to explain all of the experimental facts. Briefly stated, tetany is due to a withdrawal of soluble and physiologically available calcium salts from the blood and especially the nervous system. This being followed by an increase in the irritability of the nerves and secondarily the skeletal muscles.

Tetany is but one expression of the reaction of the body to the complete removal of the parathyroid gland. It is quite probable that the gland has other functions besides

its influence on calcium metabolism. Further studies especially of the period immediately following parathyroidectomy and preceding active tetany should be undertaken in order to throw more light on this problem.

TREATMENT OF TETANY

Three methods of treatment of tetany are at present available.

1. **CALCIUM THERAPY.** Intravenous injections of 4 to 5 per cent. calcium lactate or chloride almost instantly remove the hyperexcitability of the nervous system, the muscular twitchings, the tachycardia, and the tachypnea, and the animal is greatly relieved of pain. Oral administration of calcium salts is of doubtful value. Intramuscular and subcutaneous injections are followed by intense local irritation and are, therefore, contra-indicated. The intravenous injection should be slow and continued until the desired effect is produced, which will require different amounts of calcium in each case.

The same holds true for the treatment of tetany in the human. The beneficial effect of this treatment usually lasts for 24 hours or longer when symptoms of excitation begin to reappear. The life of the animals cannot be saved by the continued calcium administration and the animal usually dies with evident symptoms of cachexia and depression. The calcium treatment is, however, of value in the control of acute and temporary tetany.

2. **TREATMENT WITH PARATHYROID EXTRACT.** Vassale, MacCallum, Beebe and others have observed that the injection of the fresh extract of the fresh parathyroid (preferably from cattle) is followed by a temporary relief of the animal from tetany. Feeding the gland has no influence on tetany.

Beebe claims that the active substance is precipitated

with the nucleoprotein of the gland. This treatment is naturally troublesome, as the necessary material is not always easily available.

3. TRANSPLANTATION OF PARATHYROID. Halsted has shown conclusively that autotransplantation of the parathyroid gland is feasible provided that there is in the subject a demand for such tissue (partial or complete insufficiency). The gland can be implanted into the abdominal muscles and begins to function normally within a short time. According to Halsted isotransplantations are never successful, as the transplanted glands are absorbed. Other authors, however, claim to have succeeded in transplanting parathyroids from one individual to another.

TETANY DURING PREGNANCY AND LACTATION

In rare cases tetany has been observed in the human during pregnancy and lactation. According to Seitz tetany is usually confined to pregnancy, about 90 per cent. of the cases occurring during pregnancy and only 10 per cent. during lactation. Experimentally this subject has been approached by a number of investigators. As early as 1898 Vassale and Generali reported tetany during the first days of lactation in a bitch 18 months after extirpation of three parathyroids. The animal was to all outward appearance normal after the operation, but developed a most severe attack of tetany a few days after she had given birth to her young. The experiments of Thaler and Adler are of especial interest in this connection. They succeeded in producing tetany in rats during pregnancy by partial parathyroidectomy. However, tetany was never observed in these animals during lactation. Successive pregnancies always caused the reappearance of tetany, so that we may regard this condition as an example of latent tetany.

Gross observed tetany in a pregnant cat after extirpa-

tion of three parathyroids. The animal appeared to be normal for 25 days after the operation, when suddenly tetany set in. Twelve days later the cat gave birth to three young and the symptoms disappeared.

Similar observations were made by Erdheim, Fromme and others. Thierry and Knoll, at the suggestion of Seitz, studied the response to galvanic stimulation in pregnant women and found high values in 80 per cent. of their cases (120). The nerve irritability seemed to increase as pregnancy advanced and reached its highest point at the time of delivery. Then normal irritability was soon reëstablished. Similar observations on animals are lacking, although it would be of interest to ascertain the changes in nervous irritability during reproduction in partially parathyroidectomized animals. Fromme was able to show that the injection of extracts of placenta into partially parathyroidectomized animals caused tetany. This does not necessarily mean that the placenta is the etiologic factor in tetany during pregnancy, as Rudinger was able to elicit tetany in partially parathyroidectomized rats by the injection of tuberculin, morphine, atropine and other substances.

Whether or not calcium has any relation to tetany in pregnancy is difficult to decide. The daily calcium requirement of the fetus is relatively small in comparison to that contained in the average mixed diet. It might, however, be conceivable that when the calcium intake with the food is relatively low a deficiency of calcium in the tissues and blood might follow which might be aggravated by an existing parathyroid insufficiency. The same would hold true for tetany during lactation. We are forced to look upon pregnancy as a condition which puts an extra strain on the physiological processes of the body. Under these circumstances it is rather surprising that tetany is not a more frequent occurrence during pregnancy in the human. Dis-

eases such as beriberi and pellagra are especially common during the period immediately preceding and following childbirth. Incidentally it may be stated that pregnancy is not associated with any morphological changes in the parathyroid gland.

The experimental data seem to point to the fact that interruption of pregnancy and lactation soon removes the symptoms of tetany.

TETANY IN OFFSPRING OF PARATHYROIDECTOMIZED MOTHERS

Iselin made the interesting observation that rats born of partially parathyroidectomized mothers exhibited an abnormally high electrical irritability. Furthermore these animals seem to be especially susceptible to the effects of parathyroidectomy, inasmuch as they die 4 to 10 hours after such an operation, with most intense symptoms of tetany.

ECLAMPSIA AND THE PARATHYROID

Vassale on the basis of his experiments with parathyroidectomized animals advanced the theory that eclampsia is tetany modified to some extent by pregnancy. According to Vassale eclampsia is due to a hypoparathyroidism. However, it should be emphasized that the clinical pictures of tetany and eclampsia differ in so many essentials that this hypothesis does not seem to be reasonable. Furthermore it was shown by Seitz that the increased irritability of the peripheral nerves to galvanic stimulation, a typical and constant symptom of tetany, is not constantly present in eclampsia.

SUMMARY

1. The parathyroid gland has a definite physiological function which is still incompletely understood.

2. The presence of a minimum of parathyroid tissue in the body is essential for life and the continuation of normal metabolism.

3. Parathyroid insufficiency seems to be characterized by an increased irritability of the nervous system to the galvanic current, which may be due to the withdrawal of soluble calcium salts from the blood and tissues. Parathyroid insufficiency leads to an alkalosis which is converted into an acidosis as a result of active tetany. Definite metabolic changes take place in animals after complete parathyroidectomy.

4. Pregnancy puts an extra strain on the functions of the parathyroid, as evidenced by the appearance of tetany during this period in partially parathyroidectomized animals.

5. Tetany has been observed during lactation in animals with parathyroid insufficiency. Interruption of lactation was followed by recovery.

6. The offspring of partially parathyroidectomized animals exhibit a marked increase in nerve irritability.

7. An intravenous injection of soluble calcium or strontium salts or hydrochloric acid almost instantly removes the symptoms of tetany. However, tetany may reappear after this treatment and the life of such animals cannot be saved by the continued administration of calcium. The injection of parathyroid extract seems to have a temporary curative effect on tetany animals.

Isotransplantation of parathyroids into animals with parathyroid insufficiency is usually successful.

The spontaneous recovery from tetany in experimental animals is probably due to changes in their metabolism (acidosis) caused by the hyperactivity of the skeletal muscles during tetany.

8. The experimental facts do not support the theory that eclampsia is due to hypoparathyroidism.

9. A condition which might justly be termed hyperparathyroidism is unknown at the present time.

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THE RELATION OF THE PARATHYROID SYSTEM TO THE FEMALE GENITAL APPARATUS *

BY EUGENE H. POOL, M. D.
New York

THE parathyroid glands were first described in 1880 by Sandstroem, but no physiological significance was attached to these bodies until 1891, when Gley demonstrated their relationship to tetany. From that time extensive experimental and anatomical studies have been carried on, and it has been shown that the parathyroids are specific organs with internal secretion.

The paramount interest in the parathyroids has been dependent upon the occurrence of tetany as the result of the removal of these bodies in goiter operations. However, the technique of partial thyroidectomy as now practiced is so planned as to safeguard the parathyroids; consequently tetany is a rare sequel to the operation.

ANATOMY

The parathyroid glandules (Sandstroem) or "epithelial bodies" (Kohn) are branchial cleft derivatives. They develop from the third and fourth branchial clefts of each side as masses of compact epithelial cells. The glands are

* Parts of this article are abstracted from articles by the author which have appeared in the *International Abstract of Surgery*, May, 1915, p. 465, and *Annals of Surgery*, 1907, Vol. xlv, p. 507.

arranged in pairs, a superior and an inferior body being present on each side. They lie close to the posterior surface of the thyroid, in the majority of instances external to the surgical capsule. The bodies vary in size from about 3 to 15 mm. (Figs. 1, 2, 3.)

The blood supply of the parathyroids is derived for the most part from the inferior thyroid artery. After ligation of this vessel, the parathyroids of the same side may be supplied with blood from the superior thyroid artery, and after ligation of the superior and inferior thyroid arteries of one side, the parathyroids of that side may be supplied, through anastomoses, by the vessels of the opposite side, as well as by the pharyngeal, œsophageal, and tracheal vessels.

Nerve fibers, presumably from the sympathetic, have been demonstrated by Rhinehart in close relationship with the vessels of the parathyroids. Since he found no fibers within the parenchyma, he assumed that these were vasomotor and not secretory nerves.

Accessory organs, that is, small supernumerary glandules, have been found not infrequently in various positions in the neck, but especially below the thyroid, within the thymus, and even within the thyroid.

PHYSIOLOGY

That there is a correlation between the functions of the various glands of internal secretion is now generally believed; but in what manner and to what extent the parathyroid bodies affect and are affected by the thymus, thyroid, pituitary, adrenals and pancreas is hypothetical. The immediate object of this paper is the question of possible interaction between the parathyroids and the generative organs. The consideration of this feature will be deferred.

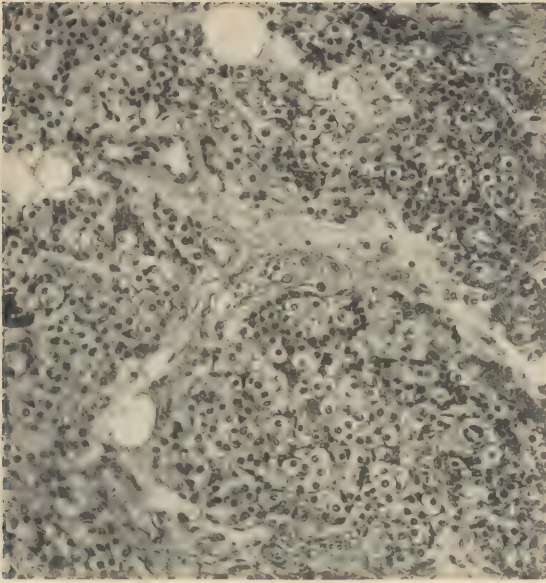


FIG. 1.—Principal cells. Photomicrograph reproduced from "Tetany Parathyreopriva," Pool, *Annals of Surgery*, 1907.

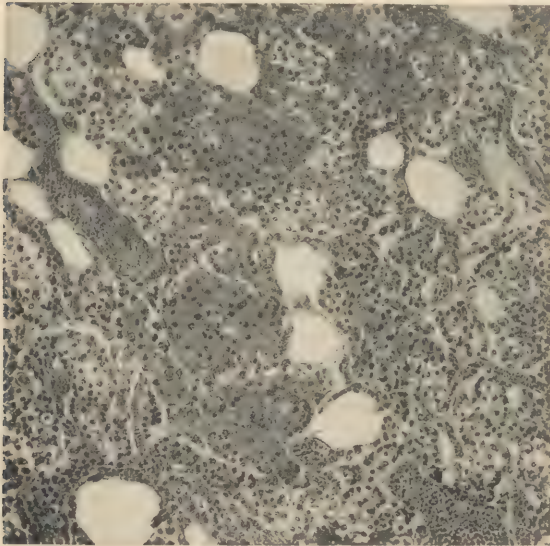


FIG. 2.—Masses of oxyphilic "functional" cells. Photomicrograph reproduced from "Tetany Parathyreopriva," Pool, *Annals of Surgery*, 1907.

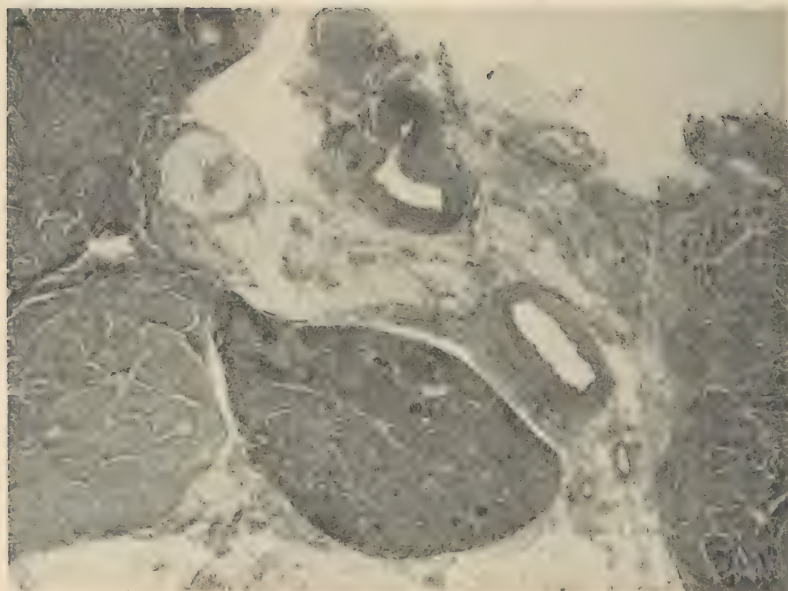


FIG. 3.—Parathyroid gland to contrast relationships of thyroid (x), parathyroid (y), recurrent laryngeal nerve (z), inferior thyroid artery (o), and esophagus (p). Pool and Falk, *Annals of Surgery*, 1916.



FIG. 4.—Method of producing leg phenomena in tetany, followed by contractures of muscles of right calf and plantar flexion of right foot.



FIG. 5.—Postoperative tetany. Arm phenomenon, showing contractures of fingers as a result of extreme abduction of arm, with elbow extended.



FIG. 6.—Leg phenomenon, showing plantar flexion of foot as a result of forcible flexion of trunk upon thighs with knee extended.



FIG. 7.—A type of contracture of hand and wrist in tetany.

The function of the parathyroids is unknown; hypotheses as to their physiology are for the most part founded upon the relationship of the parathyroids to tetany. A vast amount of experimental work has been done in this connection; the results indicate that complete removal of parathyroid tissue results in fatal tetany.

After partial removal of the epithelial bodies relative insufficiency of the parathyroid function—latent tetany—may occur. Under such conditions tetanic attacks may be precipitated in an apparently healthy animal by circumstances favorable to its development, such as pregnancy and lactation. This feature is important in the consideration of the correlation between the parathyroids and the generative organs. It will, therefore, be elaborated later.

Certain extraneous influences also affect the development of tetany. Thus, a meat diet or a cold environment appear to intensify the manifestations of tetany.

THE PATHOGENESIS OF TETANY. The hypothesis has been advanced by MacCallum, Frommer, Lundborg, Vassale, Pineles, and others that the parathyroids have an antitoxic action, the suppression of which results in the tetany reaction. By this hypothesis tetany parathyreopriva would be explained as an auto-intoxication, and one, perhaps the chief, function of the parathyroids would be the prevention of the action of certain toxic substances regularly present in the circulation.

MacCallum inclines to the belief that tetany is closely dependent upon a disturbance of the calcium content of the blood. He states that direct analysis of the blood of an animal in tetany shows it to be very poor in calcium. However, Cooke and others have questioned the importance of the calcium decrease in tetany.

As a result of the fact that in tetany parathyreopriva bases seem to be eliminated more freely and stored in less amount than under normal conditions, the hypothesis has

been advanced that the condition is an evidence of acidosis (Morel, Musser). Experimental work which is now in progress convinces me that acidosis in tetany is absent or not striking.

No constant lesions have been demonstrated in the nervous system in tetany, although much work has been done upon this phase of the subject.

RELATION OF THE PARATHYROIDS TO TETANY IN MAN. That tetany following goiter operations is usually due to the removal of the parathyroid glandules has been proved by a long series of careful experiments upon animals, as well as by significant findings of Erdheim, Pineles, and others in man. However, occasionally tetany has occurred after comparatively slight interference with the thyroid; such as enucleations, the removal of one lateral lobe and vascular ligations (Iversen). That a light tetany can develop when the four arteries are ligated is readily understood; but the fact that tetany occurs only rarely as a result of this procedure is surprising (Iversen).

How many parathyroids can support health with no evidence of parathyroid deficiency cannot be positively stated, but the best evidence indicates that two parathyroids are essential and sufficient.

It follows from an analysis of the reported cases that the occurrence, intensity, and course of postoperative tetany in man are dependent upon the amount and functional usefulness of the parathyroid tissue that is left (Guleke).

SYMPTOMS

The symptom complex of tetany was first described by Steinheim in 1830 and the name "tetany" was subsequently suggested by Corvisart. Since then the same clinical picture has been repeatedly noted in association with various conditions of widely different character. For

example, it has been seen to occur with severe gastrointestinal affections, especially dilatation of the stomach, with pregnancy and the puerperal state, with some acute fevers, with various nervous diseases and after removal of the thyroid gland. The cause of its occurrence in most of these conditions is not understood; but, as a sequel to thyroid operations, tetany has been shown to depend upon deficiency of functionating parathyroid tissue, and in consequence has been designated by Erdheim "tetania parathyreopriva." The clinical manifestations of this type of tetany are the best understood and must be taken as the standard. We will, therefore, outline them briefly.

Tetania, or tetany, parathyreopriva is characterized by certain very striking symptoms which render it practically unmistakable. The most conspicuous of these are intermittent tonic spasms of the voluntary muscles, those of the extremities being most affected. A salient feature is the *exclusive involvement of the flexor groups of muscles*. Intercurrent contractures of the facial muscles are relatively rare, and the muscles of the chest, back, and abdomen participate in exceptional cases only. The tetanic spasms are usually preceded by certain prodromata which persist for a variable period before the onset of the attack. These include headache, sensations of weakness or prostration, more or less rigidity of the limbs, radiating pains, and clonic twitchings. The contractions usually begin in the hands, and subsequently involve the feet; less often the feet are affected coincidentally or independently. The spasms are almost always, although not invariably, symmetrical and bilateral. As a rule, two or more of the fingers are flexed and the thumbs are forcibly adducted, sometimes tightly clasped by the contracting digits. The most characteristic contraction has been designated "accoucheur's hand" (Trousseau). (Fig. 5, Fig. 7.) In 50 per cent. of the cases the wrist also becomes flexed, while

flexion of the forearm with adduction of the arm to the trunk occurs infrequently. Exceptionally the fingers are held wide apart, the terminal phalanges alone being flexed. The feet, when involved, take the position of *pes equinus* or *equinovarus*, as a result of contraction of the muscles of the calf. In the contractions of tetany the affected muscles become very hard to the touch and oppose a powerful resistance to attempts at passive relaxation. Should this prove successful the tetanic attitude is at once resumed when the traction diminishes. Fibrillary twitchings are sometimes visible in the contracted muscles.

The onset of an attack is as a rule about one to three days after the operation, but this period may be less; in rare cases it may be as long as two weeks. The duration of an attack may not exceed a few minutes, or the attack may last for a number of hours; but it rarely persists as long as 48 hours. The termination of a tetanic spasm is frequently preceded by symptoms resembling those observed at the onset.

While there may be a free interval of days or weeks between the attacks, unfortunately this is far from being the rule. There are generally several attacks in the course of the day, the patient's rest at night being unbroken. In the severest cases one attack follows another with alarming rapidity. As a rule consciousness is retained during the attacks. In severe cases, extreme dyspnoea may occur.

Besides the attacks of spasms there are other manifestations of the disease. Disturbances of sensation are regularly present, especially pain, which is a frequent concomitant of the spasms. Hyperesthesia, paresthesia, or anesthesia may also be noted. Temporary redness and edema are not infrequently observed over the joints.

Further, the evidences of *chronic tetany* may develop. These consist chiefly in certain trophic disturbances, such as loss of hair, dry skin, changes in the nails, teeth, and

lens, also metabolic changes resulting in cachexia. The manifestations of chronic tetany may persist for years.

A certain number of cases, too numerous to be interpreted as accidental coincidences, present a combination of tetany with typical epileptic seizures.

Certain authors also include with the symptoms of tetany the hysterical attacks which are occasionally present.

Trousseau assumes three different degrees of tetany based upon the distribution of the spasms: first, a mild form, affecting the peripheral muscles only, some of these attacks being even limited to the hands; second, a moderate form, with involvement of the facial, abdominal, and trunk muscles; third, a severe form, extending to the involuntary muscles.

TESTS. Of particular significance as bearing on the diagnosis are the tests of Erb, Chvostek, Trousseau, and the leg test. These may be elicited during the free intervals, or latent periods, and likewise after the subsidence of the attacks of muscular spasms.

Erb's Test. There is a marked increase of galvanic irritability of the motor nerves, especially the ulnar. Hyperexcitability is evidenced by contracture to abnormally mild stimuli, KC, AC, AO, and KO all being low. A kathodal opening contraction below 5 milliamperes is particularly significant. Erb's test is undoubtedly the most sensitive, reliable, and accurate for tetany. It should always be used in a suspected case.

Trousseau's phenomenon can be demonstrated in two-thirds of all cases of tetany. The symptom consists in the occurrence of a tetanic spasm in a limb as the result of compression of its main nerve trunks.

Chvostek called attention to the facial phenomenon which can be elicited in tetanic patients by gently tapping over the area of distribution of the facial nerve. The resulting short twitchings are known as Chvostek's symptom.

In the leg phenomenon (Beinphänomen, Schlesinger's sign, Pool's phenomenon) contractures are caused by putting the sciatic nerve on the stretch. For this test the patient is placed in a sitting position, with legs fully extended upon the thighs, and the trunk is then forcibly flexed upon the thighs by pressure exerted between the shoulders (Fig. 4). The contractures are preceded and accompanied by pain, which may be severe enough to cause the patient to cry out. The feet become forcibly flexed (plantar) and adducted, assuming a position of marked equinovarus. This position cannot be altered by passive efforts however forcible. The muscles of the calf stand out conspicuously and become board-like to the touch. The onset of the pain and contractures begins from about 40 seconds to two minutes after the position is assumed. The pain may become so severe in a short time as to make it imperative to desist. The arm, tongue and Hoffman's tests are of little clinical value.

The course of tetany following thyroidectomy has been divided by Frankl-Hochwart into three classes: 1. Cases characterized by onset soon after the operation, severe course, and fatal outcome. 2. Cases in which the symptoms appear soon after the operation but subside after a variable time and are followed by recovery. 3. Cases in which the patients live, but present the manifestations of chronic tetany. It is necessary to extend this classification: thus, there may occur "latent tetany" with no muscular spasms but with positive Chvostek's phenomenon and other kindred signs (von Eiselsberg). Moreover, after the spasmodic attacks have ceased, recurrences may take place, especially under the influence of certain conditions which are practically the same as those with which the onset of idiopathic tetany is associated: namely, pregnancy, lactation, cold seasons, diet of meat, etc. (Guleke).

According to Guleke the prognosis of postoperative tetany is not good. From the cases which he compiled from the literature 25 per cent. died and 17 per cent. developed a chronic or markedly recurrent tetany. Iversen, in his compilation, found the death-rate in postoperative tetany to be about 17 per cent.

TREATMENT OF TETANY PARATHYREOPRIVA. As soon as symptoms of tetany are noticed calcium lactate should be administered, followed by parathyroid nucleoproteid. The calcium should be repeated as indicated; the nucleoproteid should be given continuously. Although benefit has been claimed for calcium lactate given by mouth in doses of about 30 gr. every four hours, intravenous administration appears to be much more efficient (20 c.c. of a 5 per cent. solution with 100 c.c. of normal sodium chloride solution). The nucleoproteid is administered subcutaneously or intramuscularly indefinitely, 1 c.c. of a 1 per cent. solution being given three times a day.

Parathyroid transplantation is indicated when medical treatment seems of no avail, or when the symptoms persist for a sufficient period to make it probable that spontaneous cure will not occur.

In view of the uncertain status of all proposed methods of treatment, the importance of prophylaxis is self-evident.

PROPHYLAXIS. In operations upon the thyroid gland, it has been shown that not merely must sufficient thyroid be left in order to prevent the occurrence of myxœdema, but that a sufficiency of parathyroids must be left so as to prevent the occurrence of tetany. The posterior part of one lobe must always be left, thus practically insuring a sufficiency of parathyroids with their blood supply. It is even safer, however, to leave the posterior parts of both lateral lobes.

ENDOCRINIC RELATIONS BETWEEN PARATHYROIDS AND THE SEXUAL FUNCTION

1. GENERAL. Experimental studies have not established a definite interaction or mutual relation between the parathyroids and the *gonads*. Partial parathyroidectomy has no influence on the histological structure and

functional activity of the ovaries and testicles according to Alquier and Theuveny. The effects of parathyroidectomy are not notably modified by an animal's sex. In this connection it is of historical interest to note Silvestri's assumption of a close relationship between the parathyroids and the ovaries on the basis of the apparent freedom from tetany of adult female animals which had been castrated prior to the extirpation of the parathyroids, whereas immature females, as well as adult male animals, died of tetany, irrespective of the performance of castration. The fallacy of this observation was shown by Massaglia, Purpura, Cleret and Gley, and recently by Meyer (1914). In all their animals death from tetany followed complete extirpation of the parathyroids even when the ovaries were removed before or after the parathyroidectomy.

The different phases of the female sex cycle, especially the latter part of pregnancy and the period of lactation, are known to exert marked influence on the production of tetanic spasms. By animal experiments, Erdheim, Adler and Thaler showed that partially parathyroidectomized animals not only developed tetany after the operation, but after recovery were again attacked in a subsequent pregnancy. Other animals which had remained free from symptoms of postoperative tetany presented such symptoms in later gestations. That is, the pregnant state elicited tetanic spasms in the presence of diminished parathyroid function. In other words diminished parathyroid function creates a tendency to tetany, which may not manifest itself until pregnancy supervenes.

Pregnant animals have been shown to react much more markedly to experimental lesions of the parathyroids than nonpregnant animals. (Erdheim.) The total removal of the parathyroids causes pregnant animals to abort and to die after a shorter period and under more violent tetanic symptoms, than nonpregnant animals. The effects of par-

tial extirpation serve to show that *during pregnancy more parathyroid tissue is needed for the preservation of life as well as for the avoidance of tetany than under ordinary conditions*. The obvious conclusion is that the parathyroid function is relatively strained in the course of pregnancy.

The disturbances of the internal secretions, as related to pregnancy, childbirth, and the puerperium, were discussed at the Fifteenth German Gynecological Congress, by Seitz, who emphasized, with special reference to the parathyroids, that although no distinct morphological changes have as yet been demonstrated in these organs, the tetany of pregnancy is probably referable to parathyroid insufficiency.

2. OFFSPRING OF PARATHYROIDECTOMIZED ANIMALS. The effect of total parathyroidectomy upon the power of procreation has been studied by Guleke in rats in which postoperative tetany takes a chronic course. These animals did not procreate after total parathyroidectomy. Animals whose parathyroids have been only partially removed, however, may conceive and carry their young to term, although abortions and still births are common. In a large number of the cases the young die in the first few days after birth. According to Vassale, the milk of tetanic animals is often abundant, and instead of harming the young, causes them to develop better than others from the same litter which are raised on cow's milk.

3. PARATHYROID FUNCTION AS AFFECTED BY THE SEX CYCLE IN THE FEMALE. During *menstruation* the entire endocrinic system is probably in a state of heightened activity. A failure of adjustment on the part of the parathyroids to this increased metabolism may lead to evidence of insufficiency with occasional culmination in the clinical picture of tetany. This is shown by case reports of Hoesslin and Lundborg. Following goiter operations,

their patients suffered from tetanic spasms at each menstrual period. In contrast to these cases in which the menstrual processes elicited tetanic attacks in predisposed women, are observations on young girls suffering from idiopathic tetany who promptly recovered with the first establishment of the menstrual flow, and on older women whose tetanic symptoms disappeared at the beginning of a menstrual period. Moreover, occasionally, tetany has been known to occur primarily as a sequel to menstruation, sometimes manifesting itself after each menstrual period. It is difficult to draw conclusions from the evidence at hand further than to state that a tetanoid state and chronic tetany tend to aggravation about the menstrual periods.

Parathyroid lesions have recently been held responsible for puerperal eclampsia by Vassale, but this view is opposed by others, notably by Seitz, on the ground of negative tests of galvanic nervous irritability in a number of eclamptic patients. Moreover, no morphological proof has been adduced to the parathyroid theory of puerperal eclampsia. According to the investigations of Allegri, and others, the parathyroid glands appear practically normal in these cases.

4. **MATERNAL TETANY** (tetany during pregnancy and the puerperium). Tetanic spasms occurring in connection with the childbearing processes, represent one of the oldest known forms of the disease. Trousseau described the condition in 1854 as "contractures des nourrices," but it had already been recognized by Dance and Steinheil (1830-31). An important contribution to the subject by Frankl-Hochwart contains 53 cases from the literature and 23 personal observations. Opinions differ as to the relative frequency of gestation, puerperal and lactation-tetany respectively. The puerperium and the suckling of the child are held by some to be far more responsible than the pregnant state, but it is maintained by others, notably Seitz, that from 80 to 90 per cent. of the cases begin before

childbirth, while only a small number occur exclusively during lactation. The time of predilection for the onset of tetany appears to be in the second half of pregnancy, beginning with the sixth month, but the contractions may appear in the early months or during parturition.

A disturbance of parathyroid function must be held responsible for maternal tetany. The clinical picture of the disease corresponds accurately to that of tetania parathyreopriva. The dependence of maternal tetany on insufficiency of the parathyroids has been shown by means of animal experimentation as well as by observations upon strumectomized women who after the removal of a goiter were attacked by tetany in later pregnancies.

A twofold explanation was advanced by Chvostek, in 1905, for the existence of a special predisposition to tetany during gestation and in the puerperium: The parathyroid function, he argues, may be taxed to an increased degree by the child-bearing processes; or it may be damaged by unknown influences (since shown possibly to be a relative impoverishment in calcium salts), the result being a condition equivalent to partial removal of the parathyroids. When the parathyroid function is inadequate in the presence of pregnancy, tetany supervenes, although under ordinary conditions the diminished functional capacity of these organs may be compatible with health. This view is supported by the subsidence of the tetanic symptoms after delivery or at the end of lactation.

In the consideration of maternal tetany recent writers lay emphasis upon the supposition that the function of the parathyroids is dependent upon a sufficiency of calcium. Although it has been shown by MacCallum that the calcium content of the blood is lessened in tetany and that calcium is of therapeutic value; in other words, that insufficiency of the parathyroids is associated with deficiency of calcium; it has not been proved, that diminished calcium in the organism produces incapacity of the para-

thyroids. Nevertheless theories based upon this assumption are plausible and will be outlined.

As pointed out by Kehrer, the tissues, more particularly the central nervous system, may be deprived of their calcium contents through an increased calcium excretion in body fluids, such as blood, milk, or urine; or through a neutralization of the calcium by acids. A reduction in the calcium contents of the body is physiological, within certain limits, in pregnant and puerperal women; but, it is assumed, once this limit has been exceeded, tetany is likely to appear when the parathyroids are imperfectly developed or functionally deficient. In pregnancy, the calcium of the maternal organism is drawn upon for the structure of the fetal tissues. During parturition, calcium is lost with the blood. The nursing mother loses calcium with the milk. If it is accepted that the parathyroids are incapacitated by lack of calcium, the significance of all these physiological conditions is identical: The calcium impoverishment of the organism imposes a tax upon the parathyroid function, with the result that tetany may supervene in women having hypoplastic or otherwise deficient parathyroid glands.

The existence of a "subtetanic" condition is now assumed, by Seitz and Thierry, on the basis of important investigations, in 10 per cent. of all women during the last months of pregnancy or in course of childbirth.

The galvanic irritability of the nerves was found to be increased in the last months of gestation in eighty per cent. of the seventy healthy pregnant women examined and a still further increase of nervous irritability was found at the time of birth. In ten per cent. of the women examined such a degree of electric irritability was found during childbirth as is otherwise noted only in tetany; during the puerperium, the irritability returned to normal. It is noteworthy that with a single exception none of the examined women had suffered from tetany.

Latent tetany has been claimed by Kehrer to be more common in pregnant and puerperal women than is usually assumed. In his experience, positive findings were noted in

75 per cent. of the cases, in the latter half of pregnancy as well as during the first ten days of the puerperium. Kreiss found a positive Chvostek phenomenon, with galvanic hyperirritability of the facial nerve, in 60 per cent. of all pregnant women, and in 8 per cent. of all puerperal women. The recognition of incipient tetany has been based upon such symptoms as tingling sensations in the hands and feet, Chvostek's facial phenomenon, and galvanic hyperirritability.

Recurrent tetany has been noted not infrequently in successive pregnancies, and there is a tendency for the symptoms to become more severe with each pregnancy and to occur in earlier months. Some women are entirely well during the intervals, while others suffer from a more or less severe chronic type of the disease.

The *course* of maternal tetany is extremely variable. In the great majority of the cases, the tetany of child-bearing women is of a mild type and the patients recover. Trophic disturbances of the skin and its appendages are common and are usually referred to toxins circulating in the blood. The most serious sequel is represented by catarract formation, the general nutritional disturbances apparently possessing special etiological significance in this respect. Women suffering from maternal tetany are apt to be weak anæmic individuals, many of them weakened by a considerable number of pregnancies and births in rapid succession.

In the severest cases, representing the fulminating type of maternal tetany, which may terminate in death at the height of the attack, the onset is sometimes abrupt, with marked dyspnœa, cyanosis, and loss of consciousness. Life is endangered through the possible extension of the tetanic spasms to the diaphragm and respiratory muscles. Laryngospasm is an occasional cause of death. The mortality of tetany in pregnant women, according to Seitz, amounts to 7 per cent. In the experience of Marek, of ten mothers with tetany, nine of them multiparæ, three died.

The tetany of pregnancy in some cases persists during the puerperium; in others the attacks subside in the first few days after birth. In her next pregnancy, the patient may be again attacked, or this pregnancy may be normal and she may remain free from spasms until a later one. Some women are entirely well during the intervals, while others suffer from more or less severe chronic tetany. The occurrence of premature labor may rapidly terminate the disease in pregnant women.

A case of tetany which has come under my observation is of interest in connection with the consideration of maternal tetany. (*Annals of Surgery*, 1912, lvi, 804.)

The woman, 27 years of age, has undergone 3 operations for goiter by different surgeons, 5, 10 and 12 years ago. I am informed that at the third operation, February 1, 1912, the right lobe was removed *in toto*, only the isthmus being left. The left lobe of the gland had evidently been excised at a former operation, as inspection of that side is said to have revealed no evidence of thyroid tissue. The healing of the wound was uncomplicated.

On the third day after operation tonic contractures occurred with cramp-like pains in the fingers and hands, which assumed the position known as accoucher's hand. The patient also had cramp-like pains in the calves.

On the fourth day calcium lactate was given hypodermically. Tonic contractures of the fingers of the left hand with cramp-like pains lasted from 9 P. M. to 1 A. M.

I saw the case for the first time on the next day and made various tests, finding an astonishingly marked hypersensitivity of the motor nerves as indicated by Erb's, Trousseau's, Chvostek's tests and the leg and arm phenomena.

On the sixth day, implantation of a parathyroid removed from a young male in an operation for simple goiter. The implant was placed in the properitoneal tissue behind the right rectus sheath.

Seventh day, forcible contractures with severe pains in the parts affected. The elbows were flexed at a right angle; wrists and fingers were also forcibly flexed. The attack continued from 5 A. M. to 11 A. M.

No further attacks of tetany were noticed up to the time of the patient's discharge. Shortly after her discharge she had one brief attack lasting about a minute, characterized by pain and contractures in right calf.

The woman subsequently married and passed successfully through two pregnancies.

April 7, 1913, baby born. August, 1913, baby died (intestinal disturbance); was nursed until time of death; never presented evidences of tetany. In August first menstruation since confinement; also first tetany since the brief attack after discharge from hospital following transplantation.

November 3, 1915, second child born. During pregnancy mild attacks of tetany. February, 1916, first menstruation. Had severe tetany, had to go to bed for two days.

Since August, 1913, patient has had mild attacks of tetany with each menstrual period. Patient is much worse in cold weather. If hand is put in cold water, it assumes the accoucher's position. Second baby has always been healthy; has never presented signs of tetany.

5. LACTATION-TETANY. The designation "rheumatic contracture of nursing women" was proposed in 1854, by Trousseau, for a condition observed by him in a number of cases. Loss of parathyroid competence is in general held responsible for lactation-tetany as well as for other forms of tetany connected with the female organs of generation. The onset of tetany, after childbirth, is less common in mothers who do not nurse their children, than in nursing mothers. The tetany is said to be caused by the prolonged secretion of calcium-containing milk. In women suffering from a mild form of chronic tetany, the disease sometimes becomes aggravated during lactation. Tetany has been known to occur within the first week after childbirth, and also after a latent period of two to eight months. This form of tetany has less tendency to recurrence than gestation-tetany, the proportion, according to Kehrer, being as 25:8. Whereas lactation, according to Meinert, plays a more important rôle in the

etiology of maternal tetany than does gestation, it is claimed by Seitz that from 80 to 90 per cent. of the cases begin during pregnancy and that only a relatively small number have their origin during lactation.

6. RESEMBLANCE OF CLINICAL PICTURE OF MATERNAL TETANY TO THAT OF TETANY PARATHYREOPRIVA. The remarkable conformity of the clinical pictures of maternal and postoperative tetany first led to an investigation of parathyroid insufficiency as the possible underlying cause. The dependence of maternal tetany on a disturbed function of the parathyroids has been illustrated, both by animal experiments and by observations upon women who after the extirpation of a goiter were attacked by tetany in later pregnancies. In support of this view, an interesting observation was made by Kehrer on a V-para who died on the twelfth day of the puerperium a few days after being attacked by tetany. Instead of the four normal parathyroids, the autopsy showed only a single parathyroid gland, and even this was reported as apparently abnormal.

7. TETANY IN GYNECOLOGICAL DISEASES AND AFTER GYNECOLOGICAL OPERATIONS. In cases of uterine fibromyomata and purulent endometritis tetanic spasms and tetanoid conditions have been reported.

Thus, a woman of 28 years, observed by Kehrer, while suffering from a profuse purulent discharge, complained of dragging and tingling sensations with painful tension in both hands and feet. The reflexes, especially the knee-jerks, were very lively, and Chvostek's phenomenon was well-marked on both sides. After two days' administration of calcium the symptoms suddenly subsided and did not reappear.

As a sequel to *uterine curettage* and *major gynecological interventions* tetany develops in rare instances. It is sometimes definitely preceded by a tetanoid condition. As a rule, the spasms make their appearance immediately, or

soon after the operation. For good descriptions of these postoperative tetanies we are indebted to Kehrer in Germany and Stein in this country. The gynecological interventions after which tetany has been observed, include curettage for uterine hemorrhage and incomplete abortion, ventral fixation of the uterus, plastic operations on the perineum, colporrhaphy, extirpation of vaginal cysts and of ovarian tumors. A few illustrative cases will be summarized:

Gross describes the case of a woman 39 years of age, whose uterus was curetted after abortion in the second month. At the beginning of the operation, the patient underwent a typical attack of tetany. About nine months later, the uterus was again curetted, on account of persistent menorrhagia; a similar attack of tetany followed. Reference is made to the presence of a hard nodule, the size of a walnut, in the region of the thyroid gland.

Typical tetanic spasms were observed by Goth, immediately after the performance of a plastic operation on the perineum, in a IV-para 25 years of age; the spasms were repeated about every three hours, lasted from two to five minutes, and caused rather severe pains. Both hands were held in the accoucheur-position, and the feet and toes in plantar flexion. The last attack of tetany occurred on the thirteenth day following the operation.

In a case reported by Kehrer, a woman 41 years of age, typical tetany occurred in connection with reposition of a retroflexed myomatous uterus, under light ether anæsthesia.

8. TETANY IN THE NEWBORN. A relation between infantile tetany and disturbed parathyroid function is suggested by the conformity of the clinical manifestations with those of tetania parathyreopriva. Typical tetany of the newborn manifests itself soon after birth in the offspring of tetanic or tetanoid mothers, and the children rarely survive longer than a few weeks or months. The infants of tetanic mothers sometimes suffer from typical tetany, but often have merely the so called "tetanoid"

symptoms, especially a well marked Chvostek phenomenon. The infant's condition is probably due to prenatal causes. An increased tendency to tetany was noted experimentally by Iselin in the young of parathyroidectomized animals. In all the cases of tetany in the newborn observed by Kehrer the children were born after an easy labor, without instrumental assistance, and the convulsions could not be referred to obstetrical traumatism. Serial sections of the parathyroids of eight older children who had died from tetany were made by Habersfeld, in whose opinion the disturbances of growth and hypoplasia of the organs, with subsequent functional insufficiency, may be the result of hemorrhage into the substance of the glands.

Tetany of the newborn usually attacks weakly and premature infants. In the five cases reported by Kehrer, the disease made its appearance within the first week after birth. With one exception, the children recovered after large doses of calcium; the death occurred on the third day after birth, under symptoms of acute tetany. In the experience of Kocher and Frankl-Hochwart, children of tetanic mothers succumbed to convulsions at a very early age. According to an observation reported by Peters, in 1898, convulsions were the cause of death in nine of ten children of a mother who was attacked by tetany in the latter half of her second pregnancy and in every following gestation. The tenth child of a tetanic mother observed by Meinert, died at the age of nine months, after having suffered from convulsions since the fourth month. In another case reported by the same author, the sixth child of a tetanic mother was attacked on the eighth day after birth by convulsions of progressive severity, and died at the age of six weeks. A woman 31 years old, observed by Zirm, was attacked in the eighth month of pregnancy by painful spasms in both forearms and hands: the child died of convulsions at the age of two weeks. The infant of a tetanic mother 26 years of age, who during her pregnancy had suffered from convulsions at about a fortnight's interval, died of convulsions on the third day of life. (Zirm's second case.)

THE TREATMENT OF MATERNAL TETANY. The requirements are efficiently met by the administration of calcium in large doses. Details as to the therapeutic employment of calcium have been given under the treatment of tetany parathyreopriva.

Implantation of parathyroids has not been tried in these cases, but has been performed, apparently with some success, in tetania parathyreopriva. Internal treatment with parathyroid extract has been reported as exerting a favorable influence upon the tetanic spasms. "Immunity serum" was employed by Kehrer in a case of lactation-tetany; it had been prepared by withdrawing blood from the tetanic mother and injecting it into another woman. The serum was obtained from this woman a few days later and injected under the patient's skin with beneficial results according to the report.

CONCLUSIONS

1. No direct relationship has been established between the parathyroids and the female sex organs; no morphological changes in the parathyroids have been noted during pregnancy; yet apparently there is a connection between the parathyroids and the *sex processes* in the female.

2. Tetany, the clinical evidence of insufficient parathyroid function, is somewhat prone to occur in menstruating, pregnant and puerperal women, as well as patients suffering from gynecological diseases or who have undergone gynecological operations.

3. The cause of maternal tetany is now referred to parathyroid insufficiency.

4. The function of the parathyroids is apparently closely connected with calcium.

5. There is reason to believe that maternal tetany and lactation tetany are associated with calcium deficiency.

6. Latent tetany, or a subtetanic condition, is much more common in pregnant and puerperal women than is usually assumed.

7. Tetany in newborn infants, the offspring of tetanic mothers, is usually fatal within a short time after birth.

8. In the treatment of maternal tetany, the administration of calcium in large doses is followed by beneficial results in the great majority of the cases.

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THE THYROID GLAND IN RELATION TO GYNECOLOGY AND OBSTETRICS

BY DAVID MARINE, M. D.
Cleveland, Ohio

THE relation of the thyroid to the sex organs in the female is the most ancient and classical illustration of the interrelation of the function of glands with internal secretions. Known to the ancients in its crudest external manifestation, a subject of their daily gossip, it has passed down through the ages. Even today, in spite of the records of thousands of observations and experiments, we must confess to a very meager insight into the fundamental physiological processes involved.

Experimental approach is difficult. The lower animals lack the obvious manifestations seen in man. The search for hormones, chemical activators and depressors is still in its infancy. However, many facts of importance are known and I shall review some of them on the following pages.

Of the several possible tissues whose activities may be concerned, the thyroid, adrenal and sex glands appear most important. The adrenal medulla is important because of the effect of its hormone on all sympathetic nerve endings; the adrenal cortex because embryologically it is identical with the interstitial cells of the ovary. Both the adrenal cortex and interstitial cells are characterized by a high lipin content, the physiological rôle of which is

unknown, although there are many facts to indicate that it is of great importance. Both tissues reciprocate in their physiological hyperplasias, and reasoning from analogy with the male, these lipin rich interstitial cells probably play an important rôle in the development and maintenance of the secondary sexual characteristics.

Ancestrally the thyroid exists in the chordates in two forms—as an elaborate ventral midline pharyngeal glandular groove, the so called “Endostyle” in all the lower chordates,—Tunicates, Amphioxus and Ammocœtes (larval lampreys), and as the familiar ductless thyroid in all higher chordates,—adult lampreys, fish, amphibians, reptiles, birds and mammals. Fortunately the animal (lamprey) in which the transition from endostyle to thyroid can be followed, still exists, otherwise this extraordinary metamorphosis could not have been established.

The thyroid then is primarily a pharyngeal gland, probably closely related both to digestion and respiration and in the thyroid of higher animals, all its known activities are still intimately related to metabolism. Variations in size, within physiological limits are characteristic of all three of these tissues. In man, the dog, the cat it is the thyroid which shows the largest variations, while in rabbits the adrenal cortex and ovaries show greater variations in size than the thyroid.

It is usually stated that the thyroids in women are larger per unit of body weight than in men. This is in general true, so far as anatomical statistics can go, but it has misled some authors to imply that the difference is inherent, while in truth it is acquired and can be entirely controlled.

All the known physiological activity of the thyroid is associated with iodine. Used in ignorance from the most remote times in the form of sponge ash, sea-weed, crude salt, etc., in the treatment of thyroid enlargement, dis-

covered as an element in 1811 by the Frenchman Courtois, first knowingly used in medicine by the Geneva physician, Coindet, in 1820, it remained for Baumann, of Freiburg, to discover it as a normal constituent of the thyroid in 1895. Iodin is usually present only in traces in the thyroid at birth, unless the mother has been given iodine, when it is enormously increased. In the normal gland there are wide variations in the iodine content. The average is about 2/10 per cent. of the dried weight or from 10 to 15 mgm. in the whole gland. The iodine containing hormone is bound with the globulin of the colloid from which Kendall has recently been able to separate it by alkaline hydrolysis and to obtain it in crystalline form. Its chemical nature is unknown, though Kendall thinks it is a di-iodo-indol.

In general the iodine of the thyroid varies with the amount of colloid. Iodine is markedly decreased in the developmental stages of all goiters and following the administration of its soluble salts it is almost instantly taken up by the thyroid. Physiologically this iodine containing hormone is the most powerful activator of metabolism known. This effect appears to be brought about through stimulation of the oxidation processes, and if the work of Asher and Flack and of Cannon and his co-workers is confirmed the influence of epinephrin is very important in augmenting its action and *vice versa* the influence of the thyroid hormone greatly augments the pressor activity of epinephrin. With our present knowledge we attempt to explain the instances of increased functional activity of the gland on the basis of an increased demand for thyroid activity or what amounts to the same thing, an increased demand for the iodine containing hormone.

Thyroid enlargements appear to be compensatory or work hypertrophies and are readily controlled or prevented by the administration of very minute amounts of

iodin. Removal of the thyroid is followed by similar basic symptoms in both young and adult animals. They all depend upon depression of the various activities of tissues and a decrease in total metabolism. In the young, this change manifests itself in arrested growth and development, sexual, somatic and mental—the so called cretin. In the adult, loss of sexual functions, increased fatty deposits, mental deterioration, anæmia and malnutrition of all the tissues are the most prominent manifestations. There is no evidence of selective action or that certain organs or groups of organs are more affected than others. Superficially this might seem to be the case because certain symptoms, like those of the nervous system or genital system, are more obvious and earlier recognized.

Removal of the thyroid like removal of the ovaries or adrenals is usually accompanied by persistence of the thymus, spleen enlargement, enlargement of the lymph glands and a lymphocytosis. Nothing is known as to the cause of these changes. Removal of a large portion of the adrenals in rabbits causes slight, though definite hypertrophy of the thyroid and lymphoid hyperplasia. This is also seen in Addison's disease in man, and might be explained as part of the adrenal-thyroid interrelation.

Removal of the adrenals also causes hypertrophy of the interstitial tissue of the ovaries in rabbits, and removal of the ovaries causes hypertrophy of the adrenal cortex or even of subcutaneous transplants of adrenal cortex.

Removal of the ovaries in animals probably tends to decrease the activity of the thyroid. There is no evidence that this is a direct effect. The various attempts to establish a direct relationship between the thyroid and ovaries by a comparison of the influence of extracts on metabolism have given negative or doubtful results. Through the study of cryptorchids, and experiments of ligating the vas deferens it has been definitely established that the interstitial

lipin rich cells of the testes largely determine the male secondary sexual characters. In the case of the ovary it is not possible to separate the oogenic cells from the interstitial cells, but the attempts thus far made suggest that these cells play a very important and similar rôle in the secondary sex characters of the female.

Nevertheless, it is an outstanding fact that in man thyroid hyperplasia is many times (6 to 8) more common in the female during and after adolescence than in the male during and after adolescence. Up to this period sex makes no difference in the incidence. Congenital goiter is not influenced by sex and in all the lower animals sex likewise has no influence, the incidence remaining the same at all periods of life.

In the human subject the period when thyroid enlargements most frequently occur are at puberty, during menstruation and during pregnancy. During each of these periods the body metabolism is increased and as it is a major function of the thyroid to stimulate oxidation processes in the body, it is probable that the heightened metabolism is of thyroid origin and the enlargements of the thyroid at these times are true work hypertrophies. This view is supported by the facts that supplying the iodine containing hormone artificially or even iodine, from which the gland can elaborate its own hormone in increased amounts, prevents the hypertrophy, and in any developing hypertrophy of the gland the iodine is decreased. In rut and pregnancy of the lower animals these changes are too slight for certain detection, though many authors have reported mild degrees of thyroid hypertrophy in both rut and pregnancy. I have given considerable attention to the study of this feature and have never been able to detect any change in size, histological appearance or iodine content greater than the range of changes found normally in either sex unassociated with sexual activity. An

increase in metabolism occurs in animals also during rut and pregnancy and, therefore, some increase in thyroid activity is probable, but it is too slight to be recognized by morphological or chemical changes in the thyroid as can often be done in man.

The degree of change in the thyroid during puberty, menstruation and pregnancy is normally slight, amounting to no more than the enlargement incident to the increased blood supply. Occasionally hypertrophy of the epithelium occurs and always there is some decrease in the iodine content. Cellular hypertrophy is not possible until a great drop in the iodine has taken place. In the dog, ox, sheep, pig and man it has to fall to less than .1 per cent. as compared with a normal of over .2 per cent. of the dried weight. These anatomical changes are identical with those which occur in developing goiters, and in goiter districts it is at these periods that simple goiter most frequently develops. The development of great enlargements of the thyroid at these periods merely means the coincidence of the cyclic sexual factor with the continuously operating causal agent of simple goiter and must not be confused with the slight increase in activity or better, the slight temporary insufficiency of the thyroid of sexual origin.

It is possible that the same chemical disturbance initiates the thyroid change, both in sexual activity and in simple goiter, the difference being one of degree. This is purely a speculation, for the experimental work so far has furnished no suggestive lead as to the exciting cause of either. Nor has the study of menstrual disturbances, of the pathological physiology of pregnancy or of diseases of the genital tract thrown any light on the nature of the thyroid reaction associated with sexual activity.

The extensive study of the relation of the sex glands to

Basedow's disease likewise, has given no clue to the nature of the thyroid sex gland interrelation; though the incidence as regards sex is similar to that of simple goiter.

To summarize, it may be stated that there is evidence in man of a thyroid sex gland interrelation recognizable in the female in association with the development of secondary sexual characters, with the menstruation and with pregnancy and also in the male at puberty, but to a very slight degree. The meager evidence available would tend to indicate that the interstitial cells of the ovary and perhaps, also, the adrenal cortex play a major rôle in this relation in the female, as certainly the cells of Leydig do in the male.

The thyroid enlargement is of the nature of a work hypertrophy to stimulate metabolism identical in appearance and so far as we know, different only in degree from that seen in simple goiter. Both of these reactions can be controlled and prevented either indirectly by giving iodine or directly by giving the iodine containing hormone in physiological doses.

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THE THYMUS GLAND AND ITS POSSIBLE RELATION TO THE FEMALE GENITAL TRACT

BY ALWIN M. PAPPENHEIMER, M. D.

New York

INTRODUCTION

THE vigorous research that has been expended upon the thymus gland during the past few years has not, on the whole, been very fruitful. That the thymus serves an important function, especially in the growing organism, cannot be doubted. The organ is conspicuously large, has a characteristic structure, which is maintained with but slight variations in all classes of vertebrates, reacts in a very definite way to a variety of injuries, and has a constant relation to the development of the sexual organs. There are, furthermore, obscure but undeniable correlations with thyroid, adrenal and possibly other organs of internal secretion. Although these general facts seem established, yet in every detail of structure and physiology there has been, and is, the greatest conflict as to facts and interpretations.

It is, indeed, no easy task to find one's way about through the maze of conflicting statements, and it is particularly difficult, in the present state of our knowledge, to draw any far reaching conclusions as to the importance of the thymus in relation to the disorders of the female genital tract. In preference, I shall try to present a brief

general oversight of our present knowledge of the thymus, based upon a critical study of the work of others, and upon my own studies in this field, and shall then review, somewhat more in detail, the work which bears upon the relation of the thymus to the genital organs.

I. ANATOMY AND HISTOLOGY

There is at present very satisfactory agreement in regard to the finer structural features of the thymus. Through the studies of Hammar¹ and of Maximoff² and his pupils we have come to regard the thymus as an epithelial organ invaded by lymphocytes from the adjacent mesenchyme; these proliferate within the gland and come later to form the bulk of the thymus tissue. The epithelial component, however, persists as the reticulum and enters throughout the formative period into the peculiar cell complexes known as the Hassal bodies.

The thin walled bloodvessels which penetrate the lobules from the interlobular septa are accompanied by sheaths of connective tissue, but there is no general fibrous reticulum such as is present in lymph glands. The framework, in the meshes of which lie the thickly crowded lymphocytes, is formed by the branching and anastomosing epithelial cells.

The genesis and nature of the small thymus cells has been much discussed. It has been maintained by Stöhr, on histogenetic grounds, that, in spite of their resemblance to lymphocytes, they are in reality epithelial in origin and nature. This view is still accepted by Mietens,³ Schridde,⁴ Fulci,⁵ and others; but the balance of opinion is greatly in favor of their being true lymphocytes. Morphologically the small thymus cells are identical with lymphocytes to the last detail. They show typical amœboid mobility

under suitable conditions. Their complete independence of the epithelial constituents of the gland has been demonstrated in tissue cultures by the writer⁶ and by Wassèn.⁷ Under these conditions the small thymus cells wander out early into the plasma, and degenerate within a relatively short time, being phagocyted by the epithelial elements, and showing no proliferative capacity. The epithelial cells, on the other hand, after a latent period of 24 to 36 hours, show active growth into the plasma, often in the form of coherent sheets of cells, a manner of growth that we are accustomed to regard as characteristic of epithelium.

I have lately been able to bring further evidence in favor of the biological identity of the thymus lymphocytes with those from lymph glands.⁸ A cytotoxic serum prepared by immunizing a rabbit with thymus lymphocytes both agglutinates and cytolizes suspensions of lymphocytes. On the whole, therefore, we may regard it as assured that the thymus is a lympho-epithelial organ in which the two types of structures coexist in the most intimate relation. Indeed, one cannot doubt that there must be some purpose in this symbiotic relation. Even in the normal gland the fragile lymphocytes are constantly destroyed and replaced, and the whole cells or fragments of their nuclei taken up and digested by the epithelial cells; and this process goes on apace under a variety of pathological conditions.

II. THE THYMUS AS A SECRETORY GLAND

What histological evidence have we that the thymus is a secretory gland in the ordinary sense? Mitochondrial granules and filaments can be demonstrated in the lymphoid cells, and occasionally larger droplets, some of them lipid in nature, are found in the epithelial cells and larger

cell complexes which enter into the formation of the Hassal bodies. There is no evidence that these are secretory products. The histological structure, however, does not in the least suggest a typical glandular arrangement, as exemplified in the thyroid, parathyroid, the anterior hypophyseal lobe, the adrenal cortex or the islands of Langerhans. The vascular supply is less abundant than in these tissues, and the capillaries do not enter into intimate relation with the individual cells.

All this speaks against the idea that the thymus elements discharge preformed secretion products directly into the blood stream.

III. DISINTEGRATION OF NUCLEAR MATERIAL

The more one studies the thymus the more certain becomes the conviction that the constant, and under some conditions, excessive disintegration of nuclear material is the most obvious form of activity which takes place in this organ. It would serve no purpose at the present time to speculate further on the meaning of this process, but here I think we shall in time find a clue to the chemical function of the gland.

IV. NORMAL DEVELOPMENT AND INVOLUTION

There is one other anatomical feature of the thymus which deserves emphasis. This is its progressive growth up to the onset of sexual maturity, followed by its subsequent involution. The recognition of this fact we owe to the painstaking studies of Hammar¹⁹ and his pupils. It holds true not only for the human thymus but for all classes of vertebrates, even the cartilaginous fishes. This well established, but by no means generally acknowledged fact, disposes at once of an enormous casuistic literature,

in which the presence of healthy gland tissue in normal amount is interpreted as abnormal persistence or hyperplasia.

V. EXTIRPATION EXPERIMENTS

Probably the most interesting part of the voluminous thymus literature is that which deals with the effect of experimental extirpation. According as one accepts the results of one or other group of investigators, the thymus is revealed as an organ indispensable to orderly growth, to the proper ossification of the skeletal system, to normal intellectual function, indeed, to continued life itself; or, on the other hand, if one remains unconvinced, the thymus falls in dignity to an organ the loss of which is readily compensated for, an organ which has no specific relation to bone formation, or to calcium metabolism in general; in short, the status of the thymus as a specialized gland of internal secretion becomes a matter of grave doubt.

I cannot review in detail the numerous experiments of this class, which began with Restelli¹⁰ in 1845, and have been prosecuted up to the present day. All the common domestic and laboratory animals have at one time or another been used as operative material, and with the most discordant results. The older work, in which asepsis was disregarded, the completeness of the operation often uncontrolled, and the possible existence of accessory thymic tissue ignored, is chiefly of historical interest.

Of those workers who have obtained definite effects from thymectomy within recent years, we need mention only Basch, Klose and Matti, all of whom have used dogs as their principal operative animal.

Basch^{11 12} found in his thymectomized puppies after a latent period of two to three weeks, an increase in softness of the bone, accompanied by arrest in growth and apparent defect in intelligence. Later,¹³ he reported the occurrence

of galvanic hyper-excitability in his thymectomized dogs, less intense, however, than in experimental parathyroid tetany.

The studies of Klose and Vogt^{14 15 16 17} have attracted much attention, and seemed for a time to have put the entire thymus question upon a firm experimental basis. Without going into details, Klose's work may be summarized briefly as follows: Thymectomy in dogs performed before the 20th day is followed by a latent period of two to four weeks, during which the puppies show normal growth and behavior. This is followed by a state of "adiposity," lasting two to three months, during which time the weight curve runs parallel to the control, but the general habitus and behavior differs from that of healthy animals. The puppies fatigue easily, the gait is awkward and waddling, the bones feel softer and more elastic. The intelligence is impaired and the behavior apathetic.

After three to four months there is said to ensue a terminal cachectic stage, ending in death after a period varying from three to fourteen months. In addition to the cachexia Klose observed marked retardation of growth, great muscular weakness, and in the terminal stage apathy, deepening into coma. A tendency to intercurrent infections, especially corneal ulcerations was striking.

As regards the specific changes in the bones which Klose and Vogt often allude to as rachitic, a critical analysis leaves one in doubt. There are many discrepancies in their descriptions which makes the analogy to true rachitic lesions doubtful. Matti,¹⁸ however, who in 1912 repeated Klose and Vogt's extirpation experiments on dogs, described and pictured in his animals lesions which are unquestionably rachitic. Whether these bone changes are to be regarded as due to a lack of thymus secretion, as Matti holds, is another question.

As regards the effect of thymectomy in animals other than dogs, the results, as has been stated, have been contradictory. In white rats Klose,¹⁹ Magnini²⁰ and Flesch²¹ have obtained positive results comparable with those of Klose in dogs.

There is then a massive array of experimental work in favor of the view that the thymus is an essential organ, exerting a controlling influence upon growth and bone formation. In spite of conflicting details the importance of the thymus appeared to rest on a firm basis. As

Lampè²² has said, its "honor seemed to have been retrieved." Unfortunately, a number of workers have quite failed to substantiate these positive findings.

Thus, Nordman,²³ operating on dogs between the tenth and fourteenth days, using strict asepsis, tracheal insufflation, wide exposure of the mediastinum and strict histological control as to the completeness of the operation, produced neither nutritional or skeletal changes. There was no increased susceptibility to infection, no correlated effects upon sexual glands or spleen; and, contrary to the statements of Klose and others, subsequent splenectomy in these animals was well borne.

Howland, McClure and Park at Johns Hopkins University have for several years been working on this problem. Their complete results have not yet been published, but a preliminary report in 1914,²⁴ and recent personal communications, assure me that they also have obtained negative results. They, as well as Nordman, have been alive to the importance of keeping their animals under hygienic conditions.

The latest publication on the subject is that of Park²⁵ on guinea-pigs. His results in these animals were wholly negative, but he shows that the almost constant presence of the accessory thymus tissue in the guinea-pig makes this animal unsuitable for a determination of the question as to whether the presence of thymic tissue is essential to life.

My own work on rats,^{26 27} in which the thymectomy was performed on very young animals, and the completeness of the extirpation as well as the absence of accessory thymic tissue, controlled by serial sections, has convinced me that Klose and his successors are in error so far as the effects of thymectomy in this animal are concerned. In a fairly large series in which the extirpation was complete, and in which no accessory thymic tissue could be demonstrated, no difference in growth or in bone development from control animals of the same litter were found.

Furthermore, I had the opportunity of studying rachitic lesions of great severity in rats,²⁸ but these occurred not

only in completely thymectomized animals, but in those with partial extirpations, in unoperated controls of the same litter, and in unrelated animals from the stock cages. This disease, long ago accurately described by Morpurgo,²⁹ is a spontaneous one, altogether unrelated to the removal of the thymic tissue.*

My personal conviction, therefore, is that the loss of the thymus in young animals is not of prime importance, and is readily compensated for in ways that are not yet understood. I believe, further, that the disturbances in osteogenesis, so frequently emphasized in the experimental literature, are best explained by the fact that young animals, kept under laboratory conditions, are notoriously susceptible to rachitis, as well as to intercurrent infections, and nutritional disturbances of all sorts. Confirmatory evidence that the thymus is not concerned in the production of rachitic lesions is found on the autopsy table. Klose and others are very vehement in attributing the negative results of other workers to incomplete extirpations, or to the presence of unrecognized accessory thymic tissue. But in human rickets thymic tissue is always present in abundance, the amount, of course, varying with the general state of nutrition. Indeed, there are no pathological states known in man in which one finds a complete absence or destruction of the thymic tissue, so that, even if one accepts in their entirety the claims of certain experimental workers, their results seem to have little bearing on human pathology.

* There has just appeared an article by Renton and Robertson (*Journ. of Path. and Bact.*, 1916, xxi, i) entitled *Thymusectomy in Dogs and its Relation to Spontaneous Rickets*. The conclusions reached are that "spontaneous rickets gives rise to exactly the same symptoms as Basch, Klose and Vogt, and Matti attribute to thymusectomy . . . that the removal of the thymus does not make the animals more susceptible to spontaneous rickets . . . and that thymusectomy of itself does not appear to cause any symptoms."

VI. HYPERTHYMIZATION

The attempts at experimental "hyperthymization" have, up to the present, added little of fundamental importance. It has not been possible to isolate from the gland by chemical means substances having a definite physiological action. The depressor effect which follows intravenous injection of thymic extracts has been variously interpreted. It is probably not specific, and at any rate there is not the slightest evidence that the thymus *in vivo* furnishes vaso-depressive substances to the circulation. Indeed, it is hardly to be expected that injection of variously prepared extracts of such a complex tissue as the thymus can yield information of great value.

The feeding experiments of Gudernatch,^{30 31 32} which have received confirmation from the work of Romeis,³³ Kahn,³⁴ Stettner³⁵ and others, seem to indicate a stimulating influence upon the growth of frog larvæ, accompanied by an arrested differentiation. I was able to observe a somewhat similar effect upon the regeneration of the tail segments in *lumbriculus*. These effects, however, seem to be less clear cut than in the case of thyroid extract, which accelerates involution of the tadpole tail, and is at the same time toxic. At best, such highly artificial and complex experiments throw little light on the normal function of the gland.

VII. PATHOLOGICAL CHANGES

The pathological changes which take place in the thymus are, with the exception of the tumors, very simple, and may be summed up as atrophy and hyperplasia. Aside from the atrophy or involution which follows normally upon the attainment of sexual maturity, there occurs in the gland an "accidental involution," to use Hammar's

term, under the influence of the most diverse conditions, acute and chronic inanition, infection of all sorts and such special forms of injury as the x-ray. All these factors bring about, in ways that are still obscure a massive destruction of the thymus lymphocytes, with secondary reaction on the part of the epithelial components and connective tissue.

We have been engaged during the past winter in studying the reactions of the thymus lymphocytes *in vitro*³⁰ to a variety of injurious agencies, in the hope of finding some clue to the meaning of this extraordinary fragility, and the precise factors which bring it about. Many types of injury, such as changes in H-ion concentration, asphyxia, starvation, old age, specific immune sera, various chemical agencies could be shown to act harmfully upon the cells outside the body; but no hint was obtained as to the significance in the organism of this dissolution of nuclear material *en masse*. Here, however, let me repeat again, seems to be the most promising lead to an understanding of the chemical function of the organ.

VIII. HYPERPLASIA

The significance of thymic hyperplasia is as obscure as its atrophy. One should distinguish in principle at least between the mere persistence of the gland, or, better, its retarded involution, and a true hyperplasia, or increase in the number of its elements beyond the limit normal for the corresponding number for its age. Both conditions unquestionably occur. Retarded involution follows extirpation in early life, and is associated with the retention of other juvenile characteristics. It is one feature of that peculiar anatomical conformation in adults which we designate rather vaguely "status lymphaticus." I do not think it is the cardinal feature, nor that the thymus is in any way concerned, except in so far as its persistence into the third or fourth decade may be taken as an index of the

persistence of the juvenile habitus in this type of individual. Certainly no proof has yet been offered that the gland is in any way concerned in the mysterious sudden death which may overtake these peculiarly constituted persons.

A true hyperplasia, in which the weight and the amount of the parenchyma exceeds the wide normal limits of variation for the particular age undoubtedly occurs also. In the newborn and in older children one occasionally meets with thymi of unusual size. I have, for example, seen a gland of 60 gm. in a newborn, the average weight in full-term, healthy infants being from 10 to 12 gm. That such abnormally large glands may occasionally give rise to pressure phenomena seems probable, and yet the actual proof is difficult to bring, and a critical study of the casuistic literature upon thymus asthma and thymus deaths in young infants makes it clear that many of these cases are open to other interpretations. Von Sury³⁷ deserves the credit of pointing out that many of the cases of sudden death in young infants associated with suffocative attacks and clinical signs of asphyxia are due in reality to a capillary bronchitis.

My own autopsy experience at the Nursery and Child's Hospital fully confirms this point. In older children, when the weights of the glands are compared with those of healthy children dying suddenly from accidental causes, which alone should be taken as a normal standard, it will be found that glands of excessive weight are not very frequently reported.

IX. INTERRELATION WITH THYROID

The occurrence of a true hyperplasia of the thymus in the great proportion of cases of exophthalmic goiter has come to be recognized as a distinctive feature of the disease, and the recent tendency has been to make this organ

share in the production of the symptoms. Among others, Garré,³⁸ Von Haberer,³⁹ and, in this country, Halstead⁴⁰ have performed partial extirpations of the thymus, and report favorable, and in some instances remarkable curative results. Nevertheless, the experimental ground work is lacking, and the relations of the thymus and thyroid in this disease, and in the healthy economy also, are obscure. It would seem that the thymus overgrowth is but one feature of the general lymphoid hyperplasia, which probably represents a reaction to the disturbed metabolism in this disease. A solution of the problem, however, must await a more precise knowledge of the chemical functions of the lymphoid cells.

Equally unclear is the significance of the thymic hyperplasia frequently observed in acromegaly and in Addison's disease. Experimental efforts to show a clean cut relation between thymus and adrenals have lead to nothing definite. In a large series of thymectomized rats, both cromaffin tissue and cortex were found to be present in normal amount.

X. RELATION OF THE THYMUS TO GONADS

I have left to the last the proper subject of my review, the relation of the thymus to the sexual organs. The facts may be very briefly given. Most of the experimental observations, for obvious reasons, have been based upon study of the male gonads, in which the presence of spermatogenesis gives a sharply defined criterion of maturity.

First, as to the influence of thymectomy upon the development of the sexual organs. The literature on this, as on most other phases of thymus physiology, is contradictory. Paton,⁴¹ in guinea-pigs, found that removal of the thymus was followed by increase in the average weight of the testis, amounting, in one series, to 46 per cent. Yule,⁴² however, later analyzed these figures by statistical methods,

and showed that Paton's results might be due to chance variation. Furthermore, Halnan and Marshall,⁴² in a large series obtained no such effect, and Soli,⁴³ in chickens, rabbits and guinea-pigs, found the testicles in the thymectomized animals smaller than in the controls, and spermatogenesis retarded or absent. Lucien and Parisot⁴⁴ also found a transient delay in the development of the testes. Klose and Vogt, in their dogs, observed a transient hyperplasia of the testicles, followed by atrophy in the cachetic stage. Matti was unable to determine any relation between thymectomy and the onset of spermatogenesis.

The following table, which is based on a study of a small number of thymectomized and control rats, indicates no decisive influence of thymectomy upon spermatogenesis, or total weight of the testicles:

Rat.	Age.	Operation.	Weight of testicles.	Size of testicles.	Spermatogenesis.
A3	45	Thymectomy	..	4.5	No spermatogenesis.
A4	45	Thymectomy ¹	..	12.0	No spermatogenesis.
A6	45	Control	..	6.5	No spermatogenesis. More mitotic figures than A3 and A4.
B2	58	Thymectomy ²	1.51	..	Spermatogenesis.
B4	58	Thymectomy ¹	1.45	..	Spermatogenesis.
B6	58	Control	1.50	..	Spermatogenesis.
E2	68	Thymectomy ²	..	16.0	Active spermatogenesis.
E3	68	Thymectomy ¹	..	11.0	No spermatogenesis.
O1	140	Thymectomy ²	1.456	..	Active spermatogenesis.
O2	140		1.425	..	Active spermatogenesis.
O5	140	Control	1.664	..	Active spermatogenesis.
S4	104	Thymectomy ¹	1.130	..	Fairly active spermatogenesis.
S6	104	Control	0.605	..	Fairly active spermatogenesis.
U4	79	Thymectomy ¹	0.180	..	No spermatogenesis.
U7	79	Control	0.296	..	No spermatogenesis.

¹ Incomplete Extirpation.

² Complete extirpation.

I have found but one reference to the condition of the ovaries after thymectomy. Valtorti,⁴⁵ 1909, states that

removal of the thymus in rabbits is followed by degenerative changes in the ovary, namely, a scarcity of primitive follicles in the outer zone, and regressive changes in the follicles in the inner zone. These alterations which made the ovaries functionally insufficient were regarded as merely accompanying the general malnutrition of his animals.

Hewer⁴⁶ has recently attempted to demonstrate a reciprocal relationship between thymus and gonads by the use of the x-rays. She found that irradiation of the thymus region alone was followed by degenerative changes in the testes, with delay in the time when copulation was begun. The ovaries were not structurally affected. On the other hand, irradiation of the gonads was followed by alterations in the structure of the thymus, namely, the appearance of Hassal bodies, which, according to her, are not normally found in the rat thymus.

Without attempting here a detailed analysis of this work, one may bring forward certain obvious criticisms. Only small series of animals were studied, and the controls were conspicuously few. The appearance of Hassal bodies after irradiation of the testes, upon which much emphasis is laid, is of doubtful significance. Hypertrophic cell complexes and occasional fully concentrically structured Hassal bodies occur, though sparingly, in the normal rat thymus. Furthermore, glands are described as hypertrophic, atrophic and normal without giving weights or comparisons with controls. It does not appear to the writer that conclusions can be drawn from the data presented, in view of the normal wide variations.

Much greater certainty exists as regards the effect of early castration upon the thymus; and the numerous experiments of Henderson,⁴⁷ Goodall and Paton,⁴⁸ Calzolari,⁴⁹ Ranzi and Tandler,⁵⁰ Gellin,⁵¹ Halnan and Marshall⁴² are in substantial accord. There occurs regularly,

following removal of the gonads before sexual maturity, a much delayed involution of the thymus, so that the glands are enlarged in comparison with non-castrated controls of the same age. Valtorti found the same thing to occur after removal of the ovaries in young rabbits. His experiments, however, were not adequately controlled.

Nothing definite is known as to the possible mechanism which controls this relationship. It may be said, however, that in general the development of the thymus and the lymphatic tissue runs parallel to the general nutrition. Healthy, well-fed animals have large glands, diseased, ill-nourished ones have atrophic thymi. It may well be that the large size of the gland in castrated animals is related to the tendency of these animals toward obesity or over-nutrition, and is not to be taken in the sense of specific correlation of function. Eventually even in the castrated animal, the gland undergoes its normal involutional changes.

One is so accustomed to regard the thymus as an organ, the importance of which is largely restricted to the growth period, that the recent publications of Fulci⁵² evoke considerable surprise. Fulci reports that pregnancy in rabbits accelerates the regression of the thymus, but that after the birth of the young there takes place a distinct renewal of growth. Bompiani⁵³ further claims that lactation inhibits this regeneration. Observations of human cases are lacking, and I fear that it will prove difficult, for various reasons, to bring such confirmation.

SUMMARY

There are many points of interest in connection with the thymus which I have not above attempted to discuss, but it is doubtful whether even the most detailed scrutiny of the enormous literature would lead us to more satisfactory conclusions. The fundamental problems of thymus

physiology remain unsolved, and the established facts, which concern chiefly the normal and abnormal *structure* of the gland, are not such as lend themselves to clinical application.

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THE ENDOCRINE FUNCTION OF THE PANCREAS AND ITS RELATION TO THE SEX LIFE OF WOMEN

BY A. J. CARLSON, PH. D.
Chicago, Ill.

IN 1889 von Mering and Minkowski discovered that complete extirpation of the pancreas in the dog produces fatal diabetes. This has been abundantly confirmed on all species of vertebrates so far investigated. The attempts of Pflüger and others to show that the diabetes following removal of the pancreas is due, not to the absence of the pancreas, but to injury to the duodenum and nerves connecting the pancreas with the rest of the viscera, must be considered a failure. The original conclusion of von Mering and Minkowski is definitely established: the complete or nearly complete loss of the pancreas results in fatal diabetes. The more recent investigations of the condition of the pancreas in clinical diabetes (Ssoblew, Opie, Visentini, and others) have shown that in severe diabetes or in deaths in diabetes there is usually more or less degeneration of the pancreas, especially in the island tissue. The conclusion that the pancreas is absolutely essential to life and to carbohydrate metabolism is thus based both on experimental and clinical data. This conclusion is established beyond a doubt.

I. THE ISLANDS OF LANGERHANS

The part of the pancreas concerned in this function appears to be essentially the *Islands of Langerhans*. This

seems to be demonstrated by the following facts: 1. Loss of the external pancreatic secretion (by permanent fistula of the pancreatic ducts) does not induce diabetes. 2. Ligation of all the pancreatic ducts leads ultimately to complete degeneration of all the pancreas tissue, except the Islands of Langerhans, at least in animals like the rabbit and guinea-pig. Such animals with only islets do not develop diabetes unless these remnants of the pancreas are extirpated. 3. In clinical diabetes the pancreas lesions usually involve the islets. Despite these facts the view that the entire pancreas tissue is concerned in the maintenance of the capacity of the tissues to oxidize the carbohydrates is still maintained by some clinicians and biologists (cf. Lombroso). This view finds its strongest support in the fact that human diabetes may reach a fatal issue while there still remains an abundance of apparently normal island tissue in the pancreas, as determined histologically. It is possible, however, that normal function is reduced or lost before anatomical or chemical degeneration of the cells reach such magnitude that they can be detected by the microscope. This theory of identity of the function of the entire pancreas was also supported by the work of Dale, Vincent and Thomson, and others, which appeared to show that the islets represented only stages of fatigue or rest of the ordinary pancreas tissue. Laguesse, Bensley and others have shown that this is untenable. While the islets and acini develop from the same embryological anlage (the cells of the ducts), when finally differentiated, they show constant and specific structural and chemical characteristics, evidently indicating specificity of function. And there is no foundation for the view that the one tissue is or can be transformed into the other.

The number and size of the islets vary greatly in different species, as well as in individuals of the same species. In some fishes they are macroscopic (5 x 14 mm.). In man the

islets have been estimated to make up $1/25$ to $1/100$ part of the entire pancreas tissue, or a total of 2 or 3 grams. In normal animals (dog) $5/6$ of the total pancreas can be removed without inducing diabetes, so that the "factor of safety" is very great. The total number of islands in mammals appears to be fixed at or rather before birth (Bensley).

The island tissue is made up of two distinct types of cells, showing specific staining reactions, a less abundant alpha type, and a more numerous beta type (Lane and Bensley). According to Homans it is the beta cells that show degenerative changes in diabetes.

The islets develop from the undifferentiated duct cells and may or may not retain this original connection with the ducts, but in either case the blood supply of the islets is greater than to the rest of the pancreas tissue. In this respect the islets resemble the adrenals and the thyroids. In fact, blood sinuses similar to those of the adrenals have been described in the islets (DeWitt).

The islets are also abundantly supplied with nerve fibres. Groups of ganglion cells are also distributed in the body of the pancreas. The function of the nerves distributed to the islets are unknown. Some of them are undoubtedly vasomotor nerves, but others form a network between or around the islet cells, which appears to indicate a secretory or reflex function.

II. EXPERIMENTAL PANCREATIC DIABETES

Extirpation of the whole or more than $6/7$ of the pancreas leads to fatal diabetes in all animals. In birds pancreatectomy leads to hyperglycemia and death, but there is said to be little or no glycosuria, because of the relative impermeability of the renal epithelium of birds to sugar. Following the fundamental discovery of pancreatic diabetes by von Mering and Minkowski in 1889 a tremendous amount of work has been done to elucidate the nature or mechanism of this diabetes (cf. Allen, 1914). The following facts are established:

1. Hyperglycemia and glycosuria appear within a few hours after pancreatectomy and, together with polyuria and polydipsia, persist till shortly before death, even when no food is given. If the hyperglycemia of clinical or experimental diabetes is sufficiently marked the sugar appears in the saliva, gastric and pancreatic juice and in the bile.

2. The liver and the muscles become practically free from glycogen, but the essential factor appears not to be to inability to store glycogen (alimentary glycosuria) but a *greatly diminished capacity, if not complete inability to oxidize the sugar*. The respiratory quotient is therefore low. Nishi states that perfusion of the liver of pancreatectomized turtles with Ringer + glucose solution leads to some storage of glycogen in the liver cells.

3. There is marked polyphagia and generally a striking increase (15 to 20 per cent.) in the total metabolism per unit of body weight. There is no rise in the respiratory quotient after giving glucose or fructose. The increased excretion of the acetone bodies parallels the increase in the D: N (dextrose-nitrogen) ratio.

4. There is a tendency to uremia and usually some acidosis and ketonuria, but these symptoms of diabetes are, at least in the dog, not as marked as in clinical diabetes, and the completely pancreatectomized animals die apparently from extreme inanition or from intercurrent infections rather than in diabetic coma due to acidosis.

5. When the pancreas remnant is too small to maintain normal sugar tolerance and metabolism, the pancreas rest is more likely to undergo gradual atrophy than to show hypertrophy, with the end result of absolute and fatal diabetes (Sandmeyer). The incomplete diabetes in animals following extirpation of more than 85 per cent. of the pancreas can apparently be intensified, and the appearance of complete diabetes and death hastened by a liberal carbohydrate diet (Thirolloix, Allen).

6. Complete pancreatectomy leads to death in 3 to 6 weeks, in the case of dogs, irrespective of the age of the animal, while diabetes mellitus is usually more rapidly fatal in children than in adults and old people.

7. The persistent hyperglycemia and glycosuria, and the low respiratory quotient, show that the pancreatectomized

animal burns practically no sugar, yet the study of the sugar oxidation capacity of the blood and of individual tissues like the skeletal muscles, and the heart have so far revealed no difference between the normal and the diabetic animal (Claus and Embden, MacLean, McGuigan, Patterson and Starling, Macleod and Pearce). The respiratory quotient of the dog's heart averages 0.71 irrespective whether the heart is that of a diabetic or a normal dog (Starling and Evans).

Certain other features of experimental pancreatic diabetes may be noted. Epstein and Bachi claim that there is an increase in the blood volume (plasma) in dogs and cats after pancreatectomy, irrespective whether the animal is fed. Hoskins and Gunning state that in dogs after complete pancreatectomy the blood-pressure remains either normal or somewhat depressed. Reaction to adrenalin is usually augmented, to nicotine variable but usually depressed. There is no evidence that the pancreas normally exerts a depressive action on the sympathetic nervous system. They found no evidence of increase in the adrenalin content of the adrenals after pancreatectomy. There is some increase in the amount of fat in the blood.

Verzar and Fejer claim that administration of glucose during the first three or four days after pancreatectomy raises the respiratory quotient. This, if true, would indicate that the pancreas hormone persists in the blood and the tissues for several days. This is improbable. It must be remembered, however, that all the sugar of the food or from the endogenous protein metabolism does not appear in the urine even in animals and patients showing the D:N ratio of 3.65 to 1, which Lusk has designated as the index of absolute diabetes. It is not known what becomes of the retained sugar. In diabetic patients "the respiratory quotient fails to account for all the carbohydrates that disappear in the body" (Allen and DuBois).

Attempts have been made to explain the glycosuria of diabetes by the increased rate of liberation of the sugar

from some hypothetical sugar + protein or sugar + colloid combinations in the blood. The recent dialysis experiments of Van Hess and McGuigan seem to indicate that all the sugar in the blood is present in simple solution; that is, in free form, but more recently McGuigan has come out in support of the theory of Lepine, namely, that part of the blood sugar is normally in a polysaccharide state.

The carbohydrate tolerance varies greatly in different species. It is very low in the pig and the sheep (Carlson and Drennan, Hunter and Hill). In normal persons 400 to 500 gr. of glucose may be given by mouth without inducing polyuria or glycosuria (Taylor and Hilton). In normal men and animals the oxidation of sugar is increased in proportion to the quantity of sugar given intravenously up to a very high limit (Woodyatt).

The endeavor to determine how absence of the pancreas causes diabetes is practically a record of repeated failures. The leading idea in all this work has been the internal secretion theory, or that the pancreas yields some substance to the blood in some way necessary for the oxidation of the sugar by the tissue cells. But in the absence of conclusive demonstration of internal secretion the possibility that the work of the pancreas in maintaining normal sugar metabolism consists of detoxication processes must always be kept in view. The fact that even temporary glycosuria is not induced in normal animals by diabetic blood does not render the detoxication hypothesis untenable.

The method of attack introduced by Cohnheim has not yielded consistent results (Claus and Embden, McGuigan) in the light of the findings of Levene and Mayer the method itself is called in question, as it appears that in a mixture of muscle extract and pancreas extract glucose is polymerized, not oxidized. No light on pancreatic diabetes has so far been shed by studying the sugar oxidizing power of tissue debris, or tissue extracts.

A. ATTEMPTS TO CONTROL EXPERIMENTAL DIABETES.

1. *Feeding Pancreas or Pancreas Extracts.* Feeding dogs in complete or partial pancreatic diabetes with fresh pancreas increases the glycosuria and acidosis (Sandmeyer, Pflüger, Lüthje, Beach, Rosenberg, Kirk). Cooked pancreas gives negative results. Feeding of raw muscle, liver, or other tissue extracts have the same unfavorable influence on the glycosuria and ketonuria. Ausset, and particularly Pratt, Spooner and Murphy report good effects from feeding pancreas in partially diabetic dogs, but the improvement in the carbohydrate tolerance was slight, variable, and practically negligible.

According to Massaglia feeding pancreas extract to guinea-pigs with experimental reduction of the pancreas reduces or prevents the alimentary glycosuria following carbohydrate food. He advocates the use of pancreas extract in mild cases of human diabetes.

2. *Injection of Pancreas Extracts.* Subcutaneous or intraperitoneal injections of extracts of the pancreas variously prepared may cause a temporary diminution of the glycosuria in diabetic animals (Caparelli, Vanni, Tiberti and Fanchetti, Minkowski, Hedon, Scott, Allen, Murlin and Kramer, and others). But this temporary diminution of the output of sugar in the urine is associated with the toxic effects of these extracts, such as depression, fever, etc., and McGuigan has recently shown that anything which causes marked systemic depression (such as injection of proteoses) leads to hypoglycemia, and will thus temporarily diminish glycosuria, if present. Thus Underhill reports diminution of glycosuria in dogs by hydrazine. The after effects of pancreas extracts given to diabetic animals are a general increase in the glycosuria and ketonuria (Leschke). Knowlton and Starling, and MacLean and Smedley reported that the sugar oxidation of the heart from a diabetic animal is almost nil, and in any event

much less than that of a heart from a normal animal. But further work has shown these results to be due to faulty technique (Patterson and Starling). Extracts of the pancreas added to the perfusion solution has no effect on the respiratory quotient of the diabetic heart (Starling and Evans). *There is no evidence that any extract of the pancreas so far prepared has increased the power of a diabetic animal or patient to oxidize sugar.*

3. *Blood Transfusion.* If the pancreas controls the oxidation of sugar in the tissue by a hormone or hormones, these must be present in the blood, and unless they are extremely unstable or present in very minute traces, it should be possible to increase temporarily the sugar oxidation in diabetic animals and patients by transfusion of normal blood in sufficient quantities. But the results obtained by this method are both conflicting and difficult to interpret.

Lepine reports a temporary diminution in the output of sugar in the urine, but no diminution in the blood sugar. This would seem to point to some injurious action of the foreign blood on the kidneys a suggestion also advanced by Hedon, but Rabens has shown that transfusion of normal blood into diabetic dogs does not influence the output of any of the urinary constituents except the sugar. Hess injected intravenously 50 to 150 c.c. of blood from diabetic dogs into normal dogs (on the theory that diabetic blood might stimulate the pancreas to a greater output of internal secretion) and nine to fourteen hours later he injected the serum from this animal into diabetic dogs. The influence on the glycosuria of the diabetic animal was slight or inconstant. In view of the results of Drennan, it seems likely that in the experiments of Hess the pancreas hormone in the blood was destroyed by the delay in centrifuging the blood. Alexander and Ehrmann injected blood from the pancreatic duodenal vein of normal dogs in diabetic dogs, but obtained no definite or constant decrease of the glycosuria.

Drennan injected 50 to 150 c.c. of fresh defibrinated dogs'

blood into the veins of diabetic dogs and invariably obtained a temporary lowering of the urine sugar and D: N ratio. Defibrinated sterile blood loses this action on standing for a few hours. The course of the blood sugar in the injected animals was not studied. Hedon has reported a very extensive series of blood transfusion in diabetic dogs. Direct transfusion from a normal dog into a diabetic dog previously bled dry causes a temporary lowering of the blood sugar and decrease or complete suppression of the glycosuria, but since the same results were produced when blood from a diabetic dog was transfused into another diabetic dog Hedon concludes that the temporary diminution of the hyperglycemia and glycosuria following the transfusion were not due to any specific pancreas secretion in the blood but to a lowering of the blood sugar by dilution and to a toxic action of the foreign blood on the kidneys. Hedon concludes that the internal secretion of the pancreas acts on and is absorbed by the liver, and is therefore not present in the blood of the systemic circulation. Hedon attempted to obtain evidence in support of this view by introducing a living pancreas in the systemic and in the portal circulation of diabetic dogs. With the living pancreas interposed in the portal circulation the hyperglycemia and glycosuria were diminished, but interposed in the general circulation the pancreas had no effect. We do not think that these later results of Hedon can be accepted, in view of what is known concerning the carbohydrate metabolism in dogs with Eck fistula. In the animal with the Eck fistula the internal secretion of the pancreas, if there is one, must pass into the general circulation, and only a small part of it can reach the liver by way of the hepatic artery, just as in Hedon's diabetic dogs with the living pancreas from another dog interposed in the general circulation; yet the Eck fistula dog does not develop diabetes.

Murlin and Kramer have recently reported one experiment with transfusion of normal blood into a diabetic dog, using the respiratory quotient as a measure of sugar oxidation. The average R. Q. for two one-hour periods before the transfusion was 0.678; for four one-half hour periods after transfusion 0.700. No conclusion can be based on the result of a single experiment, but so far as they go in this case, the transfusion raised the R. Q.

Carlson and Ginsburg found that the transfusion of normal blood into dogs in complete pancreatic diabetes without anesthesia or previous hemorrhage causes a temporary (4 to 8 hours) lowering of the hyperglycemia and the glycosuria. Similar transfusions of diabetic blood into diabetic dogs have no effect on the hyperglycemia. There was no indication in our results that the sugar retained by the animal in consequence of this temporary lowering of the sugar excretion by the kidneys is subsequently eliminated by the kidneys as an excess sugar.

The blood transfusion as such does not impair the kidneys' activity in any demonstrable way, either in diabetic or in normal dogs. The temporary lowering of the glycosuria of pancreatic diabetes by transfusion of normal blood is due to the diminished hyperglycemia, not to kidney injury, but it remains to be demonstrated that this retained sugar is actually oxidized by the tissues. The sugar might be eliminated into the digestive secretions and destroyed by the bacteria of the digestive tract.

Perfusing the Living Heart (dog). With Locke's solution previously perfused through a living pancreas, A. H. Clark has recently reported a series of experiments which seem to indicate that the living pancreas yields a substance (ferment) to the Locke's solution which enables the heart to oxidize as well as to condense the dextrose of the perfusing fluid. This pancreatic substance is destroyed by boiling, and quickly loses the activity on standing, as previously reported by Drennan.

4. *Parabiosis.* Experimental symbiosis or parabiosis of two mammals is accomplished usually by union of the skin and abdominal walls of two sisters or brothers. It was originally thought that such a union of two animals would lead to a direct vascular connection between the two, but it is now known that this is not the case. There is no fusion of the capillary system of the two animals in the region of the tissue union. But the capillary system of the two animals are in such close contact that chemical substances injected into one animal soon appear in the blood of the other animal. On the basis of this fact one

may reasonably expect that the blood hormones of one animal would find their way into the body fluids of the other animal.

On this theory Forsbach extirpated the pancreas in one member of two such parabiotic pairs (dogs). In each case a slight temporary glycosuria appeared in both animals. But because of accidents both experiments were terminated before definite results were obtained.

5. *Pregnancy.* It was shown by Pearce that the islets of the pancreas appear early in fetal life. No diabetes or glycosuria appears in human infants born two or even three months before term. This would seem to show that the pancreas hormones become of functional importance to the fetus a considerable time before the end of gestation. On the basis of these facts Carlson, Drennan, Orr and Ginsburg made complete pancreatectomy in pregnant bitches near term. *In all cases where the operation is not followed by abortion, the blood sugar and the urine remain normal until the pups are born, or removed by Cæsarian section.* Complete pancreatectomy in bitches in early pregnancy leads to abortion, or at least to death of the fetuses, in one or two weeks and the course of the diabetes is not influenced.

This absence of diabetes may be due either to the pancreas hormones of the fetuses passing into the mother's blood or to some detoxicating action on the part of the fetal pancreas.

There is a seeming discrepancy between these results on pregnant dogs and the usual clinical experience on the effects of pregnancy on the course of diabetes in women. The clinical reports are nearly unanimous on the point that pregnancy augments the diabetic symptoms, and hence the practice to terminate the gestation in diabetic mothers. But Eshner reports a case in which the diabetes (glycosuria (?)) of 2 or 3 years' standing diminished to almost

complete disappearance of sugar from the urine during a pregnancy, and the diabetes reappeared in its original severity shortly after the delivery of a full-term but still-born child. Fellner suggests that the glycosuria of pregnancy is due to the action of the ovaries (hormones) on the liver, the pancreas, and the thyroid.

6. *Transplantation of the Pancreas.* Most of the transplantations of the pancreas have been mere dislocation of a portion of it, the usual method being the transplantation of the tail of the pancreas with *its circulation intact* to other parts of the abdominal cavity, or even under the skin of the abdomen. If a sufficient quantity of the pancreas is thus dislocated or thus transferred, and care is taken to retain the circulation in good condition, at least for a time, the remainder of the pancreas may be extirpated without inducing diabetes (Theroloix, Hedon, Lombroso, Minikowski). But in most cases even these transplants show a tendency to atrophy with a gradual onset of diabetes and ultimate death in complete diabetes. The external ferments of the pancreas are probably responsible for this gradual necrosis of the graft. There is no record in the literature of transplantation of pure island tissue. There is certainly greater hope of success with such tissue than with the entire pancreas. Pflüger failed to influence the diabetes of depancreatized frogs by inserting pieces of the pancreas under the skin or in the peritoneum. Pratt reports the case of one pancreas transplant into the spleen (dog) that retained its function (absence of diabetes) for six months.

III. THE RELATION OF PANCREATIC DIABETES IN ANIMALS TO CLINICAL DIABETES

In their essential features experimental and clinical diabetes are practically identical. There is the same

impairment of power to burn sugar, the identical hyperglycemia, tendency to acidosis, lowered resistance to infection, polyphagia, etc. The two types of diabetes are influenced in the same direction by dietetic and therapeutic measures (Allen). All the evidence points to the view that actual diabetes mellitus in man is primarily due to deficiency in pancreatic hormones. This does not apply to the various glycosurias (adrenalin, nervous, alimentary, postoperative, etc.) that do not involve impairment of sugar oxidation.

The main points of difference between experimental diabetes in animals like the dog and clinical diabetes mellitus in man are a lower D:N ratio and a greater increase of total metabolism, less acidosis and an increase of total metabolism in experimental diabetes, together with the fact that human diabetes frequently ends with death before there is any pronounced degeneration in the island tissue, as determined by histological methods. It would seem that, in the absence of intercurrent infections, the human diabetic patient dies from acidosis; the dog with complete loss of the pancreas dies from extreme inanition.

IV. ADMINISTRATION OF PANCREAS PREPARATION IN CLINICAL DIABETES

1. *Administrations of Pancreas Preparations by the Mouth.* Some of the earliest attempts to treat diabetes mellitus organotherapeutically were by the administration of the pancreas by the mouth. It was early largely abandoned, for the results were practically negative (Mackenzie, Wood, White, de Cereville, Willis, Williams, Rennee and Fraser, Pratt, Wood, Marshall).

A few writers (Wegele, Meyer, Cowles, Eustis) have reported favorable results. Some of these reports contain only impressions; in others the glycosuria seemed dependent upon

an infection, and varied so much in severity that it is difficult to determine what, if any, effect the treatment had. In Cowles' case the diabetes had followed an abscess of the pancreas; marked and rapid improvement is stated to have followed the eating of one to six raw pancreases of calves daily; after discontinuing the treatment the patient became rapidly worse and died.

Rennee and Fraser administered the Islands of Langerhans obtained from fish of certain species in which they occur separately, *i. e.*, distinct from the pancreas proper, to a number of diabetics; the results were negative.

Sewall found in the earlier stages of one case of youthful diabetes that the urine could be made free of sugar by the administration by mouth of infusions of raw lean beef followed after some hours by one of pancreas; neither alone was efficacious, and after some months the combined treatment failed. The method was ineffective in a number of other cases. No good results attended the use of the commercial pancreatic powder.

Under the influence of the first report of Knowlton and Starling on the effect of pancreas extract on the sugar consumption of the diabetic heart, Eustis administered 10 to 20 grains of "an active extract of the pancreas" every four hours on an empty stomach in four cases of diabetes. He reports diminution of the glycosuria in two of the patients, and no effects in the others.

There is, however, according to Falta, a small group of cases of human diabetes in which the administration of pancreas by the mouth gives good results; *this is the result of supplying the external and not the internal secretion of the gland.* Falta refers to those cases in which the pancreas is diseased, so that there is no longer an adequate secretion of pancreatic juice into the intestine; this occurs most frequently when lithiasis causes complete obstruction of the pancreatic duct. In such cases Falta states that the administration of large doses (10 grm. daily) of pancreatin gives excellent results; calcium carbonate is given at the same time.

2. *Subcutaneous and Intravenous Injections of Pancreas Preparations.* A number of attempts have been made to treat diabetes by subcutaneous and intraperitoneal injections of extracts of pancreas, with negative or injurious results. The favorable results reported by some of the earlier clinicians were shown by Pflüger and Leschke to be wholly inconclusive. The more recent attempt of Zuelzer to treat the disease by the intravenous injection of a "pancreas hormone" was shown by von Fürth and Schwarz to be based upon a very unsatisfactory theory, and by Forschbach to be positively dangerous.

Gilbert and Carnot and von Noorden have attempted to control diabetes mellitus with administration of liver preparations.

Blood Transfusion. Raulston and Woodyatt appear to have been the first to try blood transfusion as a practical therapeutic measure in man. The patient was a man in the thirties, the diabetes of several years' standing with periods of threatening coma. The blood (500 c.c.) was yielded by a two-year older brother of the patient. The experiment was well controlled. *The blood transfusion augmented all the diabetic symptoms for several days following the operation.*

V. THE RELATION OF OTHER ENDOCRINE GLANDS AND ORGANS TO EXPERIMENTAL AND CLINICAL DIABETES

In 1908, Eppinger, Falta and Rudinger advanced the theory that diabetes is not due primarily to the hypofunction of any one endocrine gland (*e. g.*, the pancreas, but to a disturbance of the hormone equilibrium of all the glands, particularly that of the pancreas, thyroid, adrenals and hypophysis. The specific influence on carbohydrate metabolism of hypo- and hyperfunction of the adrenals, thyroid and hypophysis will be discussed in the articles deal-

ing with these glands. It now remains to consider whether the hypo- or hyperfunction of any other organ beside the pancreas are capable of so reducing the capacities of the tissues to oxidize sugar that true diabetes follows. A critical analysis of the entire literature, experimental and clinical, seems to warrant the following conclusions:

1. Hypoactivity of the thyroid, the hypophysis and the gonads may slightly increase carbohydrate tolerance, although further studies should be made on this question by more accurate methods of measuring sugar oxidizing capacity. This may be in reality a thyroid factor, as there is some indication of hypertrophy of the islets, at least after thyroidectomy.

2. Excessive administration of epinephrin, thyroid extract, and possibly hypophyseal extract may induce temporary hyperglycemia and glycosuria, due to increased sugar mobilization. But there is no evidence that this glycosuria is or passes into true diabetes, that is, lowered power to burn sugar, in the absence of a direct pancreas depression. This applies also to disturbances of the nervous system.

3. The specific influence of the hypo- or hyperactivity of the adrenals, thyroid and hypophysis on the islets of the pancreas cannot at present be definitely formulated, but it is obvious that organs as necessary to life or to normal life as the parathyroids, the adrenals, the hypophysis, and the thyroid will affect the vital processes of the islet tissue, at least indirectly, through the general disturbance of metabolism and the circulation.

After a careful experimental and critical review of the entire question Allen stated recently that the "*polyglandular equilibrium doctrine of diabetes has consisted from the first of ingenious but unfounded speculations.*" We are in entire accord with this conclusion.

The attempt of Pflüger to show that diabetes is due, not to hypofunction or loss of the pancreas, but to interference of nervous reflexes from the pancreas to the duodenum and

the liver has already been referred to. Any general reflex theory of diabetes is untenable in view of the fact *that every organ so investigated continues to oxidize sugar after complete denervation*. The loss of the capacity to burn or to synthesize carbohydrates is essentially a hormone disturbance, not a reflex disturbance.

Other workers have pointed to the probable importance, direct or indirect, of the gastro-intestinal tract in diabetes. Case has recently reported a striking parallel between the severity of clinical diabetes and the degree of ilial stasis. If the ilial stasis is a primary factor this would point to intestinal intoxication depressing the pancreas as a contributory factor in diabetes.

The administration of sodium carbonate reduces temporarily the glycosuria of depancreatized dogs. This fact has led Murlin to suggest that the diabetes following extirpation of the pancreas may be due, in part, to the unneutralized HCl of the stomach secretion. Murlin and Sweet have removed the stomach in depancreatized dogs, and find that the glycosuria is less severe than with the stomach intact. But such animals are probably more depressed than cases of simple pancreatectomy and the low output of sugar may be due to this condition.

VI. THE RELATION OF THE PANCREAS TO THE SEX LIFE OF WOMEN

1. *Diabetes and Menstruation.* Diabetes tends to produce impotence and loss of the sex urge both in men and women. In women diabetes of marked severity causes amenorrhea, sterility, premature menopause, and atrophy of the uterus. In general the depression of the sex life is proportional to the severity of the diabetes. Von Noorden states that menstruation in diabetic women is variable. It may be normal, but is usually decreased. In some women amenorrhea may set in early in diabetes, while in others menstruation may persist until late stages of the

disease. The same author states that the sexual desire is usually decreased in diabetes, but in elderly women it may be temporarily increased.

These changes in the sex life of women by the diabetic condition are probably due to impairment of tissue oxidation, and not to a direct or specific relation of the pancreatic islets to the gonads. At any rate, there is no distinct influence of gonadeetomy on the pancreas. Marshall's review of the literature shows that there is no constant reduction in the total metabolism, or change in tissue oxidation after castration and spaying. Stolper claims, however, that 25 gr. of dextrose given by mouth causes glycosuria in spayed rabbits but not in normal rabbits.

2. *Diabetes and Pregnancy.* Statistics seem to show that diabetes is more frequent in men than in women. Diabetes is also more frequent in people past forty years of age. We have seen that diabetes tends to suppress sex life. These facts operate to render pregnancy in diabetic women a relatively rare phenomenon. Nevertheless, many cases of pregnancy in partially diabetic women have been recorded. By the law of chance we should expect occasional cases of diabetes developing during pregnancy, irrespective of the influence of pregnancy on the pancreas.

(a.) *The Glycosuria of Pregnancy.* All clinical workers agree that glucose frequently (1 to 4 per cent.) appears in the urine of pregnant women, otherwise normal, especially toward the end of gestation. Bayer and Reichenstein report that 30 to 80 per cent. of pregnant women show an alimentary glycosuria after receiving only 100 gr. of glucose by mouth. This seems to indicate a lowered sugar tolerance in pregnancy that may be due to impairment of the pancreatic islets. Bayer's conclusions are questioned by Scherokauer. The question of sugar tolerance in pregnancy should be settled definitely by the more accurate method of Woodyatt. Veit thinks that the

glycosuria of pregnancy is due to liver injury from the absorption of placental material. Veit's conclusion is based in part on animal experiments. The glycosuria of pregnancy has also been ascribed to an alleged excess of epinephrin in the blood. Others have pointed to nervous or emotional factors, to excess activity of the thyroid, the hypophysis, etc. Allen thinks that "the slight intoxication of pregnancy is probably the cause of the glycosuria," but he does not indicate on what organs the "pregnancy toxin" acts. According to Scherokauer the blood sugar remains practically normal in pregnancy. Fellner suggests that the glycosuria of pregnancy is due to the action of the ovaries (hormone) on the liver, the pancreas and the thyroid. The condition is of little practical importance. The primary involvement of the pancreas in the pregnancy glycosuria has not been established.

(b.) *Pregnancy and Diabetes.* The earlier observers were practically agreed (1) that pregnancy aggravates an existing diabetes in the mother, and (2) that diabetes in the mother has a very deleterious influence on the fetus.

The deleterious influence of pregnancy on the course of the diabetes in the mother is more marked in the young than in the older mothers (Geelmuyden). Hydramnios is a frequent complication. Unless the pregnant and diabetic woman is given special dietetic care a large percentage (25 per cent. to 33 per cent.) of such women develop diabetic coma shortly after delivery (Offergeld). Premature births, or abortion due to death of the fetus, puerperal infection, etc., are frequent.

The generally accepted view that pregnancy aggravates diabetes was questioned by Neuman in 1909, and still more recently by the work of Joslin. Neuman reports severely diabetic women carried through to normal delivery of healthy children and normal lactation by dietary measures. Joslin thinks that the usual aggravation of diabetes by pregnancy is due to the greater ingestion of food. He has shown that pregnancy can be carried to full term (with a normal healthy child) in partially diabetic mothers by careful regulation of the mother's diet (Allen treatment).

Hence, it is still an open question whether the condition of normal pregnancy necessarily aggravates the existing diabetes in the mother, and there is no evidence that pregnancy can induce diabetes in a non diabetic woman. *A priori*, one would expect the stress (nervous and metabolic) of pregnancy to involve the pancreas and sugar metabolism. But this fundamental question evidently must be determined by experiment.

(c.) *The influence of the Diabetic Condition of the Mother on the Fetus.* Fellner, Fruhinholz and others state that 50 per cent. of the fetuses of diabetic mothers are still-born, or so feeble that they die a short time after delivery. There is no evidence that the child of a diabetic mother is born a diabetic. The weakened condition must therefore be due to the acidosis and other disturbances of the mother. When these are controlled by dieting, the partially diabetic mother is apparently able to give birth to a child normal (Neuman, Joslin) except for a possible hereditary tendency to diabetes in later life. But this is true only in cases of partial diabetes. I am convinced that absolute diabetes (complete loss of pancreatic islets) is incompatible with pregnancy. In such condition the fetus cannot be nourished, so that death and abortion is unavoidable. But this condition is never seen in medical practice, as a completely diabetic woman probably cannot conceive.

3. *Other Conditions of Female Sex Life Possibly Related to Pancreas Function.* Glycosuria may occur associated with the disturbances of adolescence. This is probably of nervous origin, and not a direct involvement of the pancreatic islets.

In *osteomalacia*, a malady in some way related to ovarian function, the adrenalin glycosuria is diminished, according to Christofoletti and others. This is probably due to some change in the irritability of the sympathetic nervous system rather than to any change in the pancreas.

In *chlorosis* the carbohydrate tolerance is either normal or slightly greater than normal (von Noorden).

Acetonuria of Labor. For a few days following delivery there is an increase of the acetone bodies in the urine, the acetonuria being more marked the more difficult the labor (Couvelaire and Scholten). This condition is probably due to too rapid tissue destruction, or possibly to a temporary impairment of oxidation. There is no evidence that the pancreas is primarily concerned.

Puerperal Lactosuria. In a small percentage of women trace of lactose appear in the urine at the beginning of lactation. This is evidently due to passage of lactose from the mammary gland into the blood. It is not diabetes and does not indicate any involvement of the pancreas.

Pituitary Extract and Sugar Tolerance. Cushing is a firm exponent of the view that posterior lobe extract causes hyperglycemia and glycosuria. Falta, on the other hand, claims that the extract induces hypoglycemia by increasing the sugar oxidation in the tissues. There is probably no involvement of the endocrine function of the pancreas in the use of pituitary extract as employed in gynecological practice.

VII. SUMMARY

1. All evidence supports the view that some substance or hormone secreted by the Islands of Langerhans into the blood is necessary for utilization of sugar by the tissues. This function is specific for the pancreas. Other endocrine organs may influence sugar metabolism in a superficial way by altering the sugar mobilization (adrenals, thyroid), or by increasing or decreasing the rate of oxidation in the body in general. The rest of the endocrine glands cannot maintain the power of the tissues to oxidize sugar in the absence of the pancreas, and the hypo- or

hyperactivity of other endocrine glands do not produce actual diabetes in the presence of a normal pancreas.

2. While the failure of the tissues to use sugar in the absence of the pancreas is the central and definitely established fact, there are probably other primary defects involved in the development of acidosis, lipemia, increased metabolism, lowered resistance to infections, etc.

3. All the evidence points to the view that true diabetes mellitus in man is primarily the result of pancreatic deficiency (islets).

4. There is, at present, no organotherapy of diabetes, experimental or clinical.

5. There is, at present, no evidence of any specific relations of the endocrine functions of the pancreas to the gonads, male or female, or to menstruation, pregnancy, and lactation. Absolute diabetes, induced after conception, leads to death of the fetus. Absolute diabetes probably renders conception impossible. Partial diabetes under careful dietary control permits of normal sex life of women (menstruation, normal pregnancy, normal child, lactation), and pregnancy under such conditions does not aggravate the diabetes. But in the absence of such dietary control the condition of pregnancy aggravates the diabetes in the mother, and uncontrolled diabetes in the mother is extremely injurious to the fetus. There is some evidence that in late stages of pregnancy the fetal pancreas may function for the mother.

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THE EXPERIMENTAL AND CLINICAL EVIDENCE AS TO THE INFLUENCE EXERTED BY THE ADRENAL BODIES UPON THE GENITAL SYSTEM

BY SWALE VINCENT, M. D.
Winnipeg, Manitoba

I. INTRODUCTION

DURING the last twenty-five years there has been a great change in our current views about the adrenal bodies. By no means the least important department of investigation has been the comparative anatomy of these bodies, and it may be stated that our knowledge in this regard, so far as concerns vertebrate animals, seems fairly complete. This knowledge, it must be confessed, even when combined with the results of very numerous physiological investigations, has by no means answered the question, "What is the function, or what are the functions of the adrenal bodies?" but it has made clear what we mean when we refer to these organs, and has pointed the way for a far more satisfactory comparative study of their physiology. For a full account of these investigations the reader is referred to the chapters dealing with this subject in the monographs of Vincent³³ and Biedl,⁴ and also to the chapters by Poll²⁸ in Hertwig's Handbuch. Space can only be found here for a brief summary.

Comparative anatomy and comparative physiology reveal the fact that the medulla of the adrenal body is not the only representative in the animal economy of the tissue ("the chromaphil tissue") which forms it; there are numerous scattered bodies of the same nature in close

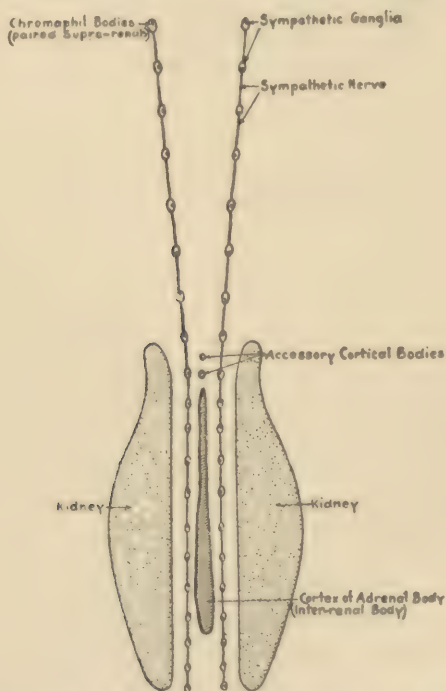


FIG. 1.—Diagram of the adrenal representatives in elasmobranch fishes showing the cortical gland (interrenal body) and the medullary glands (chromaphil bodies, "paired suprarenals") in relation to the sympathetic and the kidneys.

relation to the sympathetic ganglia and nerves in different regions. In lower vertebrate animals the medulla (chromaphil bodies) and the cortex (interrenal bodies) form two separate and independent systems, having no anatomical (and, so far as we know, no physiological) relationship to each other (Fig. 1). Indeed, strictly speaking, the

medullary substance is not part of the adrenal body at all, but simply an accumulation of the chromaphil tissue which has arisen from the sympathetic in certain abdom-

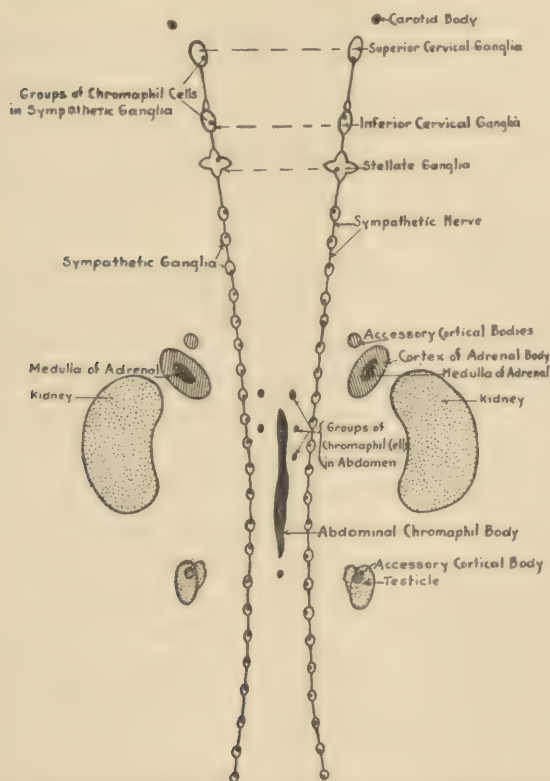


FIG. 2.—Diagram of the adrenal constituents and outstanding "cortical" and "medullary" (chromaphil) bodies in the mammal, showing the adrenal bodies, the chromaphil cells of the sympathetic, the abdominal chromaphil body ("accessory medullary") and accessory cortical adrenals in relation to the sympathetic and the kidneys.

inal segments, and has insinuated itself into the adrenal body proper, or what is usually called the cortex. So that, using the correct morphological phraseology, we ought to refer to the adrenal body and its chromaphil nucleus, or

medulla, or, according to Kohn, its "paraganglion suprarenale."

Even the adrenal cortex is not a separate and independent organ, for "accessory adrenals" are so common in many animals as to compel us to regard the adrenal cortex as part of a system in the same way as the medulla is part of a system (Fig. 2).

All this, as will be seen, notwithstanding the numerous facts which have been accumulated, renders the adrenal problem much more complex than it appeared to the earlier investigators.

In discussing the functional activities of the adrenal bodies, these facts of comparative anatomy must not be overlooked. The question which yet remains to be solved is, not what is the function of the adrenal body, but what are the functions respectively of the interrenal system (cortical system) and the chromaphil system (medullary system) which are separate and distinct in certain lower vertebrates, as, for example, in elasmobranch fishes (see Fig. 1). There seems no reason to suspect that the functions of these two systems are in any way related to each other, notwithstanding the fact that, as we approach the higher vertebrate animals, certain portions of the two come into intimate connection with each other in order to form what we call the adrenal body.

For the present, and perhaps for some time to come, it will be wise on the part of investigators to search for a separate function for each of the two systems.

EXTRACTS OF THE MEDULLA. The view adopted by the majority of modern writers in regard to the medulla (and the chromaphil tissues generally) is that it secretes a sympatho-mimetic hormone, whose function comes into play especially in conditions of emotional disturbance.

The great majority of investigations and by far the greater number of hypotheses regarding the function of

the adrenal bodies have been concerned with the secretion of the chromaphil tissue, and at the present time are centered on the physiological activities of adrenin. The cortical system, as such, has received comparatively little attention, and even plausible hypotheses concerning it are very few. The tendency of many writers has been to assume that the adrenal problem is wrapped up in the pharmacodynamical action of adrenin. But this attitude leaves out of account the significance of what we must on morphological grounds regard as the true adrenal body, that is to say, the cortex.

There is now abundant experimental evidence that it is the cortex and not the medulla of the gland which is essential to life. When the whole gland is removed, the animal usually dies within a few days, while, if the medulla only be extirpated, survival is in the majority of cases, indefinite.

EXTRACTS OF THE CORTEX. The cortex of the adrenal body does not yield any very special physiological principle to extraction. It is true that extracts made from the cortex, when injected into the veins of a living animal, will cause a lowering of the blood pressure, but this action is common to extracts made from all organs and tissues (Osborne and Vincent,^{24 25} Vincent and Sheen,^{35 36} Vincent and Cramer^{37 38} and Webster³⁹). The substance which produces this effect has been shown not to be choline. It is possible that it may be Beta-Iminazolyethylamine (Barger and Dale⁴).

The cortex also contains certain substances called "lipoids." The cortical cells contain numerous "lipoid granules," the so-called "cortical granules." Space will not permit a description of the chemical characters of lipoids. For this the reader is referred to the works of Vincent³³ and Biedl.⁴ It is not yet determined whether these lipoid granules are to be regarded as secretion

products which are about to be poured into the blood stream. Pigment granules and other cell-inclusions are also noted in certain cells of the cortex.

II. CLINICAL EVIDENCE

There are four views as to the function of the adrenal cortex:

1. That it is related to growth and development, especially of the sexual organs.
2. That it has an antitoxic function.
3. That it plays some part in the elaboration of the adrenin which is found in the medulla.
4. That the enormous development of the adrenal cortex in the human embryo is connected with the highly developed brain of man.

It is only with the first of these theories that we are here concerned. It is now tolerably certain that there is an intimate connection between sex characters and the adrenal cortex. Most of the evidence on this point is of a clinical nature.

Wooley^{40 41} and Bullock and Sequira⁶ reported that tumors or hypertrophies of the adrenal body are sometimes associated with precocious development of the reproductive organs.

Glynn¹⁰ has given an excellent account of the tumors and rests of the adrenal cortex with their relationships to sex abnormalities. The following is a brief abstract of his classification:

A. BENIGN TUMORS. CORTICAL.

Group 1. Diffuse hyperplasia passing into

Group 2. Adenomata, which may be bilateral. The cells contain a considerable amount of fat, and their arrangement is like that of the zona fasciculata.

B. MALIGNANT TUMORS. CORTICAL.

Group 1. Sarcomata: round-celled often lymphosarcoma, *i. e.*, small cells with an alveolar arrangement. These are common in children; especially males between the ages of two and three.

Group 2. Hypernephroma or Mesothelioma, a tumor having large polyhedral epithelial cells, recalling the structure of the adrenal cortex.

Hyperplasia of the adrenal gland or of accessory adrenals is frequently associated with pseudohermaphroditism. The great majority of these cases occur in female pseudohermaphrodites, that is to say, in females with internal organs of the male type, illustrating the *tendency of neoplasia or hyperplasia of the gland to be associated with the appearance of male characters in the female*. In most of the females the hermaphroditism was advanced, for prostates were present. Glynn quotes thirteen cases in illustration of this condition.

Adrenal hypernephromata are almost invariably characterized in children by precocious growth of the body generally and of the sexual organs in particular, with overgrowth of hair and fat. The skin becomes pigmented and the children are below the average in intellect. According to Guthrie¹⁵ there are two types: (1) the obese type, met with in both sexes, but apart from the development of pubic hair the development of the sex organs is not exaggerated, though one of the females menstruated. (2) the muscular or "infant Hercules" type, occurring only in males, who may show true sexual precocity.

Hypernephromata of the adrenal body in children are much commoner in females than in males, and tend to increase the male primary and secondary sexual characters at the expense of the female.

Glynn quotes six examples of the tumor referred to in the last two paragraphs. These examples were found in

young adult females and the growth was associated with changes in sex characters. It will be interesting to quote one of these (originally reported independently by Thummin³² and Bortz⁵):

A girl aged 16 $\frac{3}{4}$ years began to menstruate at 15, and continued to regularly for one year. With the cessation she grew a beard and moustache, and hair developed also on the thorax and linea alba. The voice changed to the male type. She became very obese; the mammae were well developed. She died of phlegmon of the hand. The external genitals were of the feminine type, the uterus measured 8 cm. externally and was normal, but the ovaries were small and hard, showing no trace of ovulation, neither macroscopically nor microscopically. The right adrenal contained two yellow nodular tumors the size of a cherry, and the left was converted into a mass as big as a fist. Microscopically the right tumor consisted of round or polygonal epithelial cells in a network of capillaries; those in the left showed similar structure, but the meshes were wider and more irregular. A few larger cells, rich in chromatin and often multinucleated, were also present. The condition is described as typical of "struma suprarenalis."

Gallais⁹ has recently observed and collected a number of cases in which tumors have given rise to striking abnormalities in the development of the reproductive organs. He groups them together under the title "genito-adrenal syndroma." One form of this syndrome is characterized by sexual precocity, other forms being such as are described above. He regards the cortex of the adrenal body as essentially a "puberty gland."

The subject has also been discussed by Korányi.¹⁹

III. EVIDENCES FROM COMPARATIVE ANATOMY AND PHYSIOLOGY

There are other evidences of the association between the adrenal cortex and the sexual functions.

Functional Variations. Stilling³¹ in his researches upon the adrenal body of the rabbit observed periodic vari-

ations in the weight of these organs. There was enlargement of the glands in male rabbits during the breeding season. In the same communication he reports that the peripheral part of the cortex in the frog contains during the summer certain peculiar elements, the "summer cells" which atrophy later on during the pairing season. Patzelt and Kubik²⁶ have, however, come to the conclusion that Stilling's summer cells are present the whole year round and are independent of age, sex or state of nutrition. These authors prefer to call the cells in question acidophile cells from their staining reactions. A curious point is insisted upon by these writers. They find that the acidophile cells are only present in one species, viz., in *R. esculenta*. They are entirely wanting in the adrenal bodies of the other Anura which they investigated, as also from the glands of the Urodela and the Reptilia. They note also that similar cells are found in the parathyroids of mammals and in the pituitary gland throughout vertebrates.

As far back as the year 1806 Meckel²⁰ noted a relationship between the adrenal bodies and the reproductive organs.

Nagel²³ in 1836 remarked that animals with large sexual organs and well-developed reproductive instincts possessed large adrenal bodies, which in birds and amphibians became still larger during the breeding season. According to Glynn these statements have been repeated quite recently by Aichel.¹ Glynn remarks that it is highly probable that a similar change occurs in human beings, but that there are no recorded observations on this point. He suggests that such an enlargement, if it does take place, may explain the curious tendency of any hair or "down" upon the face or body of a woman to increase in amount during pregnancy, first noted by Hegar, and confirmed by Halban.¹⁶ In the opinion of Glynn, Halban wrongly

explains this "Hypertrichosis gravidatis" by a protective action of the placenta.

A hypertrophy of the adrenal bodies during pregnancy was noted by Guieysse in the guinea-pig, which enlargement chiefly affected the zona fasciculata. According to Schenk³⁰ (quoted by Glynn) these results have been confirmed by Ciaccio and Da Costa. Gottschau¹² found that the adrenal gland as a whole measured less in pregnant than in non-pregnant animals, but that the outer zone of the cortex was increased at the expense of the inner.

Effect of Castration. Feodossiew⁸ removed the ovaries from bitches, and found that after a few weeks there was hypertrophy of the adrenal cortex, especially the zona glomerulosa. Similar results were obtained by Raineri,²⁹ but they could not be confirmed by Dick and Curtis⁷ nor by de Mira.²¹

Resemblance between Cortical Adrenal Cells and Corpus Luteum Cells. It has long been noticed that there is a resemblance between the cells of the adrenal cortex and the interstitial elements of the ovary and testis and those of the corpus luteum. Janosik¹⁸ looked upon all these cells as being very closely related. Podvissotzky²⁷ insisted specially on the resemblance between the cells of the adrenal cortex and those of the corpus luteum. This was further emphasized by Mulon²² who, from observations on guinea-pigs, goes so far as to speak of the corpus luteum of pregnancy as a temporary cortical adrenal body.

A further discussion of some of the above questions will be found in a recent work by Goñalous.¹¹

Hormone Hypothesis. It seems hopeless at present to attempt any explanation of the precise manner or the essential mechanism of the influence of the adrenal cortex upon the reproductive organs. It is perhaps most in accordance with current views to admit the hypothesis that a certain hormone, or certain hormones are secreted

by the adrenal cortex which are passed into the blood stream and so reach and exert their action upon the reproductive organs. It has been suggested that the adrenal body may act through the mediation of the pituitary, but so far as I am aware, no changes in the latter organ have been observed in any of the cases referred to above.

Much has been written and many hypotheses have been put forward on the subject of the relationships between the various organs furnishing an internal secretion. Much of this is purely hypothetical, and a great deal remains to be discovered before we can formulate any general statements.

It is possible that the simpler physiological conception of underaction or overaction respectively of the various ductless glands, now used to account for the various pathological states, may have to be supplemented or superseded by a consideration of modified or deranged function.

IV. FEEDING EXPERIMENTS

During the present year an attempt has been made to investigate the relations between the adrenal bodies and the reproductive organs by studying the effects of feeding animals with the adrenal bodies or preparations made from them.

Immediate Effects. Some years ago the present writer failed to observe any immediate physiological effect upon dogs, cats and rabbits, after feeding with the adrenal bodies of sheep; just as the administration of large doses of extracts (in some cases made from the medulla only) failed to produce any noticeable rise in the blood-pressure in the human subject (Vincent³⁴). D'Amato² has also shown that very large doses do not increase pressure, although they may cause arterial degeneration. Grünbaum,¹³ however, states that adrenal extract although it

ordinarily fails to produce elevation of blood-pressure, when administered by the mouth, will bring about this effect in cases of Addison's disease.

Effects of Continued Feeding. But the experiments about to be described are of a different character. They involve the administration of comparatively small doses of gland substance over a long period, in order to test the effect upon the growth of the body as a whole, and the reproductive organs in particular. R. G. and A. D. Hoskins¹⁷ have carried out a series of experiments on white rats in which certain of the young animals were fed with desiccated adrenal gland (Parke, Davis & Co.) while certain others were kept as controls. Forty-five rats were fed with adrenal body for varying periods of from two to nine weeks. Twenty-six animals from the same litters were kept as controls. The rate of growth and the weights of various glands were determined in each series. No differences between the two series could be detected in the case of the kidneys, heart, pituitary body, thyroid, thymus or adrenal bodies. The spleens of the experimental series were somewhat smaller than those of the controls, but highly variable in size. The ovaries in the few cases studied were larger in the experimental series. The testes (twenty-six experimental, thirteen control) showed hypertrophy. These results are in confirmation of the clinical evidence above stated, and indicate that the adrenal bodies exercise a stimulating effect on the growth of the testes in young animals.

The authors of the communication just referred to discuss the question as to what constituent of the gland the testicular hypertrophy is due to. They conclude that it is in all probability to be ascribed to the cortical portion. But it is obvious that the experiments would be more satisfactory as regards this point, if the cortex only were employed for the feeding. A series of experiments of this

type are now being carried out in my laboratory. A further criticism of the experiments above described seems justified from the fact that desiccated gland was used. I believe that the material is "degreased" before it is "desiccated," and the former process would be likely to remove many "lipoids," some of which might be among the physiologically active substances. In our experiments, therefore, we are using fresh cortex only, in order to eliminate these sources of error. We are further extending the investigation to chicks, as was suggested by Hoskins.

SUMMARY

1. What we call the adrenal body represents the anatomical association of two elements, each of which is derived from a separate and independent system. The adrenal proper, or "cortex" is part of the "cortical" or "interrenal" system. The medulla is simply an accumulation of chromaphil cells of the same nature histologically, chemically and pharmacodynamically, as similar masses of cells in other parts of the body.

2. There is no clear evidence that these two systems are functionally related.

3. The adrenal medulla (as well as the chromaphil tissue generally) is developed from the sympathetic nervous system. Its duty seems to be to facilitate the functions of this system in certain physiological emergencies.

4. The adrenal cortex (as well as the "accessory cortical adrenals") is developed from the germ epithelium, and the evidence is now strongly in favor of the view that it has certain important functions in connection with the development and growth of the sex organs.

5. There is a considerable amount of clinical evidence that tumors of the adrenal cortex are frequently associated with sex abnormalities.

6. The clinical evidence also favors the view that when cortical tumors occur in the female, an accentuation of male secondary sexual characteristics develops, and simultaneously a hypoplastic condition of the internal generative organs supervenes.

7. Additional evidence as to a connection between adrenal cortex and the sexual organs is furnished by the enlargement of the cortex during breeding and pregnancy.

8. Feeding young animals with adrenal gland substance seems to stimulate the growth of the testes.

9. It is possible that a final solution of the problem will only be arrived at when the more general problem of the relationships between the ductless glands shall have been solved.

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THE RELATION OF THE OVARY TO THE UTERUS AND MAMMARY GLAND FROM THE EXPERIMENTAL ASPECT

BY LEO LOEB, M. D.
St. Louis, Mo.

WE shall consider (1) the effects exerted on the uterus and the mammary gland by the ovary as a whole, and (2) we shall further seek as far as possible to refer to individual structures within the ovary the various functions exercised by this organ. It will therefore first be necessary to describe and analyze certain cyclic processes within the ovary itself inasmuch as its function varies at different periods in accordance with its cyclic changes.

First, we shall discuss the various structures found in the ovary and then proceed to a description and an analysis of the mechanism governing cyclic changes in the ovary. Further, we shall discuss the significance of the effect exerted by the ovaries upon the cyclic changes in the uterus and in the mammary gland and as a phase in these effects we shall especially consider the relation of ovary to uterus and mammary gland during pregnancy. This will be followed by a consideration of the influence of the ovaries on the full development of uterus and mammary gland during puberty and on the ultimate atrophy of these organs. Lastly we shall refer to the influence of the ovaries on the development of cancer of the mammary gland. In this

brief report it will hardly be possible to do much more than summarize the principal results obtained in experimental research.

I. CONSTITUENTS OF THE OVARY

1. **THE FOLLICLE.** The follicle with the ovum is the most important constituent of the ovary. Secondarily, it gives origin to two new structures, the corpus luteum and the so-called interstitial gland. After the rupture of the mature follicle the granulosa becomes transformed into the cells of the corpus luteum. We cannot wholly exclude the possibility that some enlarged theca interna cells form the periphery of the corpus luteum. In some species the corpus luteum cells multiply mitotically, in others the large size of the corpus luteum is merely due to an increase in size of the granulosa cells.¹

2. **FOLLICLE ATRESIA.** Only a very small number of follicles mature and give rise to corpora lutea. The majority degenerate, "become atretic" before maturity, but usually only after they have reached a considerable size. This degeneration of the follicles usually begins in certain species at a time, when the ova are still alive and active, and this atresia is therefore not, as has been maintained by Robert Meyer,² the result of a primary degeneration of the ovum. During this process of atresia the theca interna cells enlarge in some species of animals, become epithelioid, gland-like in appearance and remain preserved in such a state for a considerable period of time; such is the case in the rabbit.³ In other species, however, the theca interna cells remain small and have only a relatively short existence after the atresia of the follicles has set in; this latter condition we find for instance in the guinea-pig⁴ and in woman in the absence of pregnancy.⁵

3. INTERSTITIAL GLAND. In the guinea-pig where the theca interna cells of atretic follicles are not in the least gland-like and have only a transitory existence, it is not permissible to speak of the existence of an interstitial gland. There is a certain lack of clearness in the definition of the interstitial gland of the ovary, certain authors considering the presence of fat-like substances in atretic follicles as a sufficient characteristic. Such substances, however, are found in the granulosa and theca interna cells of non-degenerating as well as in theca interna cells of atretic follicles. Intracellular fat globules appear also, under certain conditions, in many varieties of other cells; therefore we usually do not consider such cells as gland cells. The size and shape of the cells and their intimate relationship to capillaries are the features most characteristic of the so-called interstitial gland of the ovary.

It has been suggested by Ancel and Bouin⁶ that in those animals in which periodic corpora lutea form, no interstitial gland exists; that it is present only in those animals in which a spontaneous ovulation does not take place. Bouin and Ancel cite the rabbit as well as the guinea-pig as animals possessing an interstitial gland. However, there is no doubt that in the guinea-pig a spontaneous ovulation takes place at regular periods, while in the rabbit it usually does not take place if copulation is prevented. This seems contradictory to the suggestion made by these authors, if we accept their statement that the guinea-pig possesses an interstitial gland. If, on the other hand, we define the term "interstitial gland" as suggested above, then the rabbit, but not the guinea-pig possesses an interstitial gland. The hypothesis of these two authors might therefore still hold good. It is readily conceivable, considering the large space required by the periodic corpora lutea, that such relationship between the presence of interstitial gland and the absence of spontaneous ovulation should exist; considering furthermore the fact that at the time of ovulation all of the medium sized and large follicles degenerate at least in certain of the species with spontaneous

ovulation. Thus at short intervals of time a large aggregation of new atretic follicles is created, which in turn necessitates the disappearance of an equal number of somewhat older atretic follicles. Under those conditions it is clear that the regular recurrence of spontaneous ovulation and the existence of a typical interstitial gland must necessarily be mutually exclusive. While some considerations thus make plausible the hypothesis of Bouin and Ancel, this relationship requires further investigation.

4. OVARIAN PARTHOGENESIS. There exists another element in a certain number of ovaries which deserves special mention. In a considerable number of guinea-pigs we discovered a relatively far-going development of the ovum, which leads to the formation of the embryonal placenta and in some cases to the development of early stages of the embryo proper (formation of the anlage of the central nervous system) within the follicle.⁷ Ultimately these structures perish, but it is important to know that parthenogenetically developing embryonal structures occur in certain ovaries, if we wish to trace to their source the various functions exercised by the ovaries. In addition we find medullary canals or cell rows which are of extraneous origin and unite only secondarily with the ovary. As far as we know no definite function can be attributed to them.

II. CYCLICAL CHANGES OCCURRING IN THE OVARIES

In the ovaries of some species well defined cyclic changes occur.⁸ They are not equally present in all species. In the guinea-pig just prior to ovulation a simultaneous, sudden degeneration of all but the smallest follicles sets in, while in other species the cyclic ovulation seems merely to lead to the formation of periodic corpora lutea without a concomitant revolutionary change in the condition of the

follicles. In still others, as in the rabbit, such regular cyclic changes are dependent on the occurrence of copulation and subsequent pregnancy. After completion of pregnancy the animal is accessible to a new copulation and a new pregnancy occurs. In this latter class of animals spontaneous ovulation without a preceding copulation does not usually take place. Again in other species copulation and pregnancy are limited to certain seasons.

1. OVULATION. The initiation of the cyclic changes in the ovary as well as the development of the corpus luteum depend on ovulation. Ovulation is probably preceded by marked changes of the circulatory conditions in the ovary, which lead to atresia of follicles. In one case, however, we apparently succeeded in producing corpora lutea experimentally without the occurrence of a spontaneous ovulation and the concomitant degeneration of follicles, by cutting into a mature follicle in the guinea-pig.⁹ In the rabbit such an experimental production of corpora lutea can be more readily accomplished according to the findings of Ancel and Bouin,¹⁰ and of Regaud and Dubreuil.¹¹

A. MECHANISMS REGULATING OVULATION. If we wish, therefore, to obtain an understanding of the cyclic changes in the ovary and of the consecutive cyclic changes in the uterus and mammary gland, we must analyze the conditions that lead to ovulation. We are now in a position to give an analysis of this process, which, while not yet complete in every particular, at least defines its principal factors.

(a.) *Retardation of ovulation by corpus luteum.* The essential factor in this process is the existence within the ovary of a self-regulating mechanism. The corpus luteum, itself the result of an ovulation, provides a mechanism preventing ovulation and therefore the production of new corpora lutea. The mechanism is automatic comparable to that regulating respiration.

Several writers such as Beard,¹² Prenant,¹³ Sandes¹⁴ and Skrobanski¹⁵ have expressed hypothetically the view that the corpus luteum might prevent ovulation. None of them attempted to give a proof of this suggestion and the majority of all investigators rejected it. Experiments on a large scale which the writer carried out without the knowledge of the writings of the previous authors, however, proved without doubt that the corpus luteum actually possesses such an influence.¹⁶

(b.) *Acceleration by removal of corpus luteum.* If at an early period of the sexual cycle we cut out all the corpora lutea, the next ovulation is much accelerated and the sexual period shortened. These experimental findings were recently confirmed by Raymond Pearl and Surface.¹⁷ They showed that injections of corpus luteum extract into fowl delayed or prevented ovulation; the number of eggs laid was considerably diminished in the injected animals. We carried out a few similar experiments on guinea-pigs. While in some injected guinea-pigs ovulation was apparently delayed, in others it took place at the expected term despite the fact that these animals had repeatedly received large doses of lutein.¹⁸ We may therefore conclude that injections of lutein extract cannot wholly take the place of the living corpus luteum. Whether or not they can do so partially in mammals, I am not prepared to say on the evidence at hand.

The acceleration of ovulation produced through extirpation of the corpora lutea is limited; the next ovulation has to await the maturation of follicles. Without the presence of mature follicles a new ovulation cannot take place even in the absence of corpora lutea.

(c.) *Copulation.* There is a third set of accessory factors of significance in the occurrence of ovulation, chief among which is copulation. The importance of this factor varies considerably in different species of animals. In the

guinea-pig it has at best only a slight significance, on the other hand, it is very important in the rabbit, where usually, despite the presence of the first two factors, ovulation does not take place without a preceding copulation.¹⁹

(d.) *Retardation by deciduomata.* There is no doubt that the presence of an experimentally produced deciduoma in the uterus (or its equivalent during pregnancy the maternal placenta—*vide infra*) as long as it is growing or at least living, has a certain delaying effect on ovulation.²⁰ This effect, however, is only present provided the corpora lutea have not previously been extirpated. If this has been done the premature ovulation occurs, even in the presence of a well developed deciduoma²¹ and, as we shall shortly see, of a maternal placenta.

We must therefore assume that the deciduoma either acts by prolonging the functioning of the corpus luteum and thus indirectly preventing copulation, or that we have to deal with the summation of the effect of corpora lutea and deciduoma under conditions in which either alone would be too weak to prevent ovulation.

But this delay is only temporary; sooner or later the ovulation takes place notwithstanding the presence of a deciduoma. Whether or not in such cases ovulation has to be preceded by the death of the greater part of the deciduoma is at present still an open question. It seems, however, that extirpation of the whole or of the greater part of the uterus even without the presence of deciduoma, may lead to a prolongation of the life of the corpus luteum and a delay in ovulation.¹⁸ Here also further investigations are necessary. Extirpation of the greater part of the thyroid on the other hand, need not be followed by a delay in ovulation in the guinea-pig.²⁰

(e.) *Prolonged retardation by corpus luteum of pregnancy.* During pregnancy the corpus luteum persists—at least in the guinea-pig—and therefore no ovulation

takes place during pregnancy. There is at present no species of animals known where ovulation occurs during pregnancy. If we extirpate the corpora lutea of a pregnant guinea-pig, however, at the time when such an interference does not necessarily lead to an interruption of pregnancy, a new ovulation occurs in the pregnant animal just as early as in a non-pregnant animal under the same conditions. Such an ovulation during pregnancy may take place without leading to abortion. It is therefore essentially the function of the corpus luteum which prevents a new ovulation during pregnancy and not the direct action of the embryo. It is possible that in certain species secondary factors active during pregnancy are added to the influence of the corpus luteum. This we would have to assume, if in some species the corpora lutea should be found entirely absent during the second part of pregnancy.

It would be of great interest to discover the factor responsible for the prolonged life of the corpus luteum during pregnancy. We suggested formerly the possibility that the embryo has such a function; however, a more recent observation makes the correctness of this hypothesis doubtful. In an early stage of an extra-uterine pregnancy experimentally produced we observed degeneration of the corpora lutea and subsequent new ovulation notwithstanding the presence of a living embryo of autochthonous origin.²¹ Furthermore, interesting experiments of R. T. Frank, who found that implantation of fetal structures into rats, which led to the production of teratomata, did not prevent degeneration of corpora lutea, point to the same conclusion.²² It is therefore in all probability not the direct influence of the embryo which prolongs the life of the corpora lutea and prevents ovulation during pregnancy. We stated above that in cases in which growing deciduomata were present in the uterus, ovulation was delayed and apparently the life of the corpora lutea prolonged. It is therefore possible that the maternal placenta plays an active rôle in preserving the life of the corpora lutea. Whether this effect is direct or indirect, perhaps by influencing of cir-

culatory conditions in uterus and ovaries, is as yet uncertain. We may consider it as very probable that the same factors which prolong the life of the corpus luteum during pregnancy, are also responsible for the greater development of the theca interna²³ and for the development of decidua-like cells in the cortex of the ovary and occasionally elsewhere in adjoining organs in woman.

(f.) *Mode of action of corpus luteum.* After we had established the significance of the corpus luteum for ovulation, two questions had still to be decided. 1. Is the effect of the corpus luteum in preventing ovulation a merely mechanical one or is it due to more complex action? 2. Does the corpus luteum prevent ovulation by interfering with the maturation of follicles or by preventing the rupture of the follicle?

As to the first question we could show that the effect of the corpus luteum is not a mechanical one. Extirpation of other parts of the ovary are without effect. Extirpation of the corpus luteum in one ovary affects ovulation in the other ovary. Inasmuch as the presence of sensory nerves in rapidly developing corpora lutea at early stages of development is improbable, we have to assume that the action of the corpus luteum is a chemical one. A substance secreted by the corpus luteum affects the follicles either directly or indirectly through influence upon the vasomotor nerves in the ovary.

As to the second question, we can state that in the guinea-pig and rabbit the corpus luteum merely prevents ovulation, and not the maturation of follicles which takes place in a normal manner.²⁴ Possibly the same factor which prevents ovulation may, in other species, as for instance in man, have the additional power of preventing the full development of the follicles. At least it seems that in man and certain other species a full development of follicles does not take place during pregnancy.²³ If the

finding of Stratz, who states that in Tupaja and some related animals well developed corpora lutea are absent during the latter part of pregnancy, is correct, then we would have to assume that some other factor rather than the corpus luteum prevents the full development of follicles, an interpretation which would harmonize well with the fact that in certain species follicles become mature during pregnancy.²⁴

(g.) *Action of interstitial gland.* We mentioned above that Ancel and Bouin⁶ assume that the occurrence of periodic corpora lutea and of interstitial gland are mutually exclusive; this would imply that animals with an interstitial gland do not ovulate spontaneously. We found that in animals with periodic corpora lutea (guinea-pig), the presence of corpora lutea leads to an inhibition of ovulation. Now, if it should prove correct that animals possessing an interstitial gland do not ovulate spontaneously, we may suggest that possibly the so-called interstitial gland is the structure responsible for this inhibition, that it increases the tonus of those mechanisms which oppose ovulation; therefore additional factors, as copulation, must come into play in order to overcome the greater strength of the inhibitive factors. At present we can regard such a statement merely as a hypothesis which may, however, deserve consideration.

III. RELATION OF OVARIAN TO UTERINE CYCLE

After this analysis of the self-regulating mechanisms within the ovary and especially of the rôle of the corpus luteum in this mechanism, and of the factors underlying ovulation, we shall next consider the relation between ovarian and uterine cycles.

The anatomist, Born, expressed, hypothetically, the view that it is the function of the corpus luteum to make

possible the nidation of the ovum in the uterine mucosa and to insure the development of the embryo. L. Fraenkel²⁵ put Born's hypothesis to an experimental test on rabbits that had copulated, by inquiring into the effects of castration and of burning out of the corpora lutea on the course of pregnancy. He came to the conclusion that castration as well as burning of the corpora lutea in the first half of pregnancy led to retrogression of pregnancy and to abortion. The number of the experiments on which he based his conclusion was, however, relatively small; furthermore, pregnancy is readily influenced by other operative and experimental procedures; and therefore in the years following Fraenkel's publication, his conclusions, as far as they concerned the effect of the corpora lutea on pregnancy, were not accepted by many, perhaps not by the majority of gynecologists, while the effect of ovariectomy was conceded if not by all, at least by the larger number of investigators. It was only several years after the significance of the corpus luteum for the uterine cycle and for the development of the maternal placenta had been established by safer methods²⁶ that Fraenkel in another publication published the results of a larger number of experiments which showed that after removal of the corpora lutea pregnancy is interrupted in a much greater number of cases than after other experimental interferences.²⁷

But even granted that the extirpation of corpora lutea during the first half of pregnancy interferes with the progress of pregnancy, such a conclusion would not give us any insight into the manner in which the corpus luteum affects the uterine mucosa. On this basis any explanation would be purely hypothetical. As a matter of fact Fraenkel did not express clearly his views as to the manner in which the corpus luteum acted on the uterine mucosa. He speaks of a softening, trophic, hyperaemising influ-

ence of the corpus luteum on the mucosa which makes it suitable for the nidation and development of the ovum. He disclaims the belief that the corpus luteum has necessarily anything to do with the development of the maternal placenta.²⁵

The experimental method used by Fraenkel was not suited to throw light on the influence exerted by the corpus luteum on the uterus. This influence could be elucidated only in experiments in which the changes in the uterus could be studied directly without the interference of a fertilized ovum. It was therefore necessary to exclude pregnancy. This we accomplished either by ligation of the Fallopian tubes soon after copulation, or by using guinea-pigs (females kept separated from males) in which heat had been observed.²⁶ In the normal guinea-pig a spontaneous ovulation takes place at the time of heat in almost all cases. The same principle was later applied by Bouin and Ancel in a somewhat modified form;²⁸ these investigators prevented pregnancy and determined ovulation by copulating female rabbits with a male whose vasa deferentia had been previously ligatured. We succeeded furthermore in substituting ordinary foreign bodies and other mechanical stimuli for the action of the ovum and thus we were able to analyze the factors that regulate the cyclic changes in the uterus and the development of the maternal placenta. Some of the principal conclusions²⁶ to which these investigations led us may be stated as follows:

1. FACTORS REGULATING THE PRODUCTION OF MATERNAL PLACENTA.

A. MODE OF PRODUCTION. If we apply certain well defined mechanical stimuli to a uterine mucosa which has been previously sensitized by the internal secretion of the corpus luteum, a maternal placenta is produced at the place of stimulation. The mechanical stimulus takes the place of the ovum. Without the presence of a mechanical

stimulus the uterine mucosa undergoes slight decidual changes under the influence of a substance secreted by the corpus luteum. We may assume that in the latter case the stimuli present in normal life and acting on a sensitized uterus produce these proliferative changes.

After the foregoing facts had been established by the writer, Ancel and Bouin²⁸ in the case of the rabbit, and ourselves²⁰ in the case of the guinea-pig, studied in detail the parallelism between the development of the corpus luteum and the cyclic changes in the uterine mucosa. The experimental production of the maternal placenta has been accomplished by ourselves and subsequently by Bouin and Ancel, Biedl and others, in the case of the rabbit and guinea-pig, and by R. T. Frank²² in the case of the rat.

It is possible to produce experimentally a much larger quantity of maternal placenta than is ever produced in life. In this as in other cases there is present a margin of reserve force which is not called upon in the actual conditions of life.

B. VARIATIONS IN RESPONSE TO THE SENSITIZING SUBSTANCE. (a.) *Quantitative.* Certain relations exist between the quantity of the chemical substance given off by the corpus luteum and the response obtained by a mechanical stimulus. The mechanical (in the case of the maternal placenta) or the metabolic stimulus (in the case of the ordinary cyclic decidual changes) elicits a response in the form of growth processes of the uterine mucosa only after the latter has received a certain quantity of this substance and has thus been sensitized. If the mechanical stimulus is applied at the time at which the corpus luteum is beginning to secrete, no growth reaction, or only a trace, is obtained. On the other hand, after the substance has fully sensitized the uterine wall, the secretion of the substance continues for a few more days and increases the

growth reaction which has now reached its maximum development. By experiments in which the uterus is transplanted at various periods of sensitization the curve of sensitization can be established and furthermore it can be proved that the secretion of the substance continues for some time after the mechanical stimulus has been applied if the optimum time has been selected. The egg fixes itself in the uterine mucosa at approximately the time when the maximum sensitization of the mucosa has been obtained.

(b.) *Non-specificity of sensitization.* The sensitizing substance is not individual—specific; the substance of one individual is able to call forth growth processes in the sensitized uterus of a different individual of the same species. But certain other substances (homoiotoxins) in the second individual cause the reaction in the strange organism to be less marked than in the organism to which it belonged.

(c.) *Specificity of deciduomata.* The sensitizing substance produces in each species specific growth reactions, which differ from those produced in other species. The structure of the experimental deciduomata in a given species corresponds to the normal structure of the maternal placenta during pregnancy. It is probably this unlikeness in the structure of the placenta in various species (dependent upon quantitative differences in the cell proliferation of various tissues and on differences in the period at which this cell proliferation sets in) that accounts for the apparent dissimilarity in readiness of response to stimuli producing artificial deciduomata.

C. LOCALIZATION OF SENSITIZATION. In the guinea-pig and probably in the rabbit the sensitization through corpus luteum substance is strictly limited to the mucosa of the uterus. In the guinea-pig deciduomata or decidual reaction can be experimentally produced only in the

uterine mucosa. With this fact accords the observation that in cases of extra-uterine pregnancy in guinea-pigs, which were found by the writer occurring in the ovaries⁷ as the result of parthenogenetic development of the egg and in a case experimentally produced on the peritoneal side of the uterus,²¹ only the embryonal placenta is produced without any reaction on the part of the surrounding maternal tissue. But while the egg can fix itself without decidua, the development of the embryo under these conditions is very much retarded and remains incomplete, and apparently the later stages of embryonal development are not reached.

It is different in women and perhaps in certain other mammals. Here we normally find during pregnancy that in the cortex of the ovary and in adjoining organs elsewhere there is a transformation of stroma cells into cells which at least resemble decidua cells. It seems furthermore that in these species decidua can be produced in the Fallopian tubes in cases of tubal pregnancy. In the guinea-pig it has so far been impossible for the writer to produce tubal pregnancy experimentally, and as previously stated in those cases in which extra-uterine pregnancy was produced or observed elsewhere than in the tube, a much delayed development occurred apparently not leading to the formation of a mature fetus. May not the explanation be that the difference in the readiness with which extra-uterine pregnancy develops in different species depends in part at least upon the readiness with which the stroma of the host responds with the production of a decidua favorable for the development of the embryo?

D. VARIATION IN PERSISTANCE OF DECIDUOMATA. (*a.*) *Without pregnancy.* Deciduomata produced experimentally have a limited existence. They usually become necrotic after a life extending over a period varying approximately between 12 and 20 days. The cyclic pro-

liferation in the uterine mucosa has a duration of only a few days. Extirpation of the ovaries or of the corpora lutea at a time when enough sensitizing substance has reached the uterine mucosa to cause production of deciduomata, in the majority of cases not only prevents the deciduomata from attaining their full size, but causes an earlier and more extensive degeneration of such deciduomata as develop under these conditions. The necroses observed in these cases are usually combined with hemorrhages and it appears that the hemorrhages are the cause of at least a considerable part of the necroses.

(b.) *With pregnancy.* On the other hand, deciduomata produced by mechanical means in one horn of the uterus, while the other horn is pregnant, show a great prolongation of life, at times through the whole period of pregnancy; this prolongation of life of the deciduoma accords with the fact that during pregnancy the decidua remains alive unless the chorionic cells of the embryo destroy it. But the behavior of the deciduomata in a non-pregnant horn of the uterus proves that this prolongation of life is not due to the direct localized effect of the embryo or chorion, but to a distant effect of either the embryonic structures or of the corpora lutea which persist during pregnancy.

Which one of these alternatives is the true cause of the prolongation of life of the deciduomata during pregnancy we cannot definitely decide. We may, however, state that if the corpus luteum should prove to be the cause of the longer life of the decidua, this effect cannot be due to a continuous elaboration by the corpus luteum of the substance which calls forth the growth of the decidua or of the deciduoma; for we can show that at a time when the life of the deciduoma is thus prolonged, the sensitizing substance is no longer produced in the corpus luteum, or is produced in such small quantities that it is no longer able

to effect a sensitization to mechanical growth stimuli. In fact, the production of this sensitizing substance extends only over a relatively short period in the early life of the corpus luteum.

We must then assume either that we have to deal with two entirely different actions of the corpus luteum, the one responsible for the sensitization of the uterus and the other for the prolongation of life of the deciduoma, or that only one substance is secreted but in different quantities at different periods of the life of the corpus luteum. A sensitization leading to the new formation of decidua would require a much greater quantity of substance than preservation of decidua already produced.

It is a well-known fact that in cases of tubal pregnancy in woman decidual changes can be found in the uterus. In this case we evidently have to deal with a similar condition. The decidual growth in the uterus initiated through the developing corpus luteum in a manner corresponding to the one found normally at a definite period of the sexual cycle in the guinea-pig and rabbit (but possibly somewhat more vigorous under the influence of the corpus luteum of pregnancy) is protected from the degenerative processes which would affect it without pregnancy, just as the deciduoma is kept alive through "distance action" during pregnancy.

IV. CYCLICAL CHANGES IN THE UTERUS

1. ALTERNATIONS OF ACTIVITY AND REST. Corresponding to the cyclic changes in the ovary a definite cycle of changes occurs in the uterus.^{28 20} This cycle includes alternating periods of activity and rest and manifests itself in changes in epithelial as well as in connective tissue structures. It is impossible at this place to attempt a description of these changes, but casual mention may be made

that in the guinea-pig, solely on the basis of these uterine changes, it is possible to determine whether an ovulation is impending or whether it has just been completed without recourse to an examination of the ovaries.²⁰ As far as the mechanism of these changes is concerned we can divide the cycle into two or more periods. The first period, comprising the heat changes in the uterus and the changes accompanying and directly following ovulation, is not only not caused by, but on the contrary is actually prevented by the activity of the corpus luteum. Preceding extirpation or degeneration of the corpora lutea is a prerequisite for this phase of the uterine cycle. It does not, however, occur in the absence of the ovary.^{26 20 16} The question, therefore, arises as to which part of the ovary is responsible for these changes in the uterus.

A. CAUSE OF HEAT AND OVULATION. For the following reasons it is improbable that the so-called interstitial gland originates this part of the uterine cycle: (a) In the guinea-pig and numerous other species, an interstitial gland in the sense in which we use this term, does not occur. (b) The analogon of an interstitial gland, the theca interna of atretic follicles is very strongly developed at periods in which heat is absent, as for instance 5 to 7 days after ovulation, and is present also in old guinea-pigs or in animals with so-called hypotypical ovaries.²⁴ (c) If we examine the ovaries of guinea-pigs at the period immediately preceding their first ovulation, we find only a relatively small number of atretic follicles, and the so-called interstitial gland or its analogon plays no significant part in such an ovary. There are, however, one or more mature follicles invariably present at the time of heat. The character of the granulosa cells of mature follicles differs in certain respects from those of ordinary large follicles. It is therefore probable that, in the absence of the inhibiting substance secreted by the corpus luteum, the mature

follicles give off the substance causing the phenomena of growth and produce the circulatory changes characteristic of this period. We have some ground for the belief that directly or indirectly the same two factors (presence of mature follicles and absence of corpora lutea) are likewise responsible for the psychical manifestations of heat in those species in which sexual desire is limited to certain periods. On the whole the psychical signs of heat are more variable than the bodily manifestations, and with the gradual development of a thought world, substituting in the individual to some extent the real world, these psychical phenomena become more or less independent of the factors to which they owe their origin. While it is thus very probable that the mature follicles are responsible for this phase of the sexual cycle, we can at the present time not altogether exclude the participation of some other constituents of the follicular apparatus.

B. CAUSE OF SUCCEEDING PHASES. The second phase of the sexual cycle stands under the influence of the corpus luteum. The corpus luteum calls forth weak decidual growth processes in the non-pregnant animal. In case pregnancy does not develop, this phase is followed by a third phase in which the corpus luteum has ceased to secrete the growth substance and retrogression of the proliferative changes of the second phase takes place. If pregnancy does take place, the proliferation proceeds to the formation of a decidua. In the fourth phase this substance is likewise absent and the uterus is resting. Even if pregnancy does occur, the corpus luteum ceases to produce the growth substance at the same time as without pregnancy. In both cases this substance is present in the guinea-pig only from the 2d or 3d to the 8th or 9th day after ovulation. The conclusion that in the third and fourth phases of the sexual cycle the growth substance of the corpus

luteum is no longer secreted, is not merely an hypothesis based on histological inferences, but has been definitely proved by us through several series of experiments.²⁶

C. INHIBITION OF CYCLICAL CHANGES DURING PREGNANCY. We saw that through the extirpation of corpora lutea a new ovulation and with it the onset of a new sexual cycle in the uterus can be accelerated. This experimentally accelerated heat and ovulation calls forth the same course of cyclic changes in the uterus which would be found in the case of ovulation at the normal time. There is, however, one exception to this rule; if in a pregnant animal all the corpora lutea are excised, the onset of a new ovulation is hastened as was stated above, but during pregnancy the accelerated ovulation is not followed by the onset of a new cycle in the uterine mucosa.²⁰ Even places of the uterine mucosa distant from the insertion of the ovum, do not undergo any of the cyclic changes noted in non-pregnant animals. During pregnancy there must therefore be present some (chemical (?)) mechanism which neutralizes the effect of the substances which affect the growth phenomena in the uterus (mature follicles (?) and corpora lutea). There is therefore a double mechanism which protects the pregnant animal from a new ovulation and its effects, namely, (a) the persistence of the corpus luteum which prevents a new ovulation during pregnancy, and (b) if this barrier should be broken there remains a second as yet unanalyzed line of defense by which the uterus is prevented from reacting in the usual manner to the growth substances produced in the ovary.

2. IS ACTION OF CORPUS LUTEUM ON UTERUS AND ON OVARY DUE TO PRODUCTION OF TWO SUBSTANCES? During the early period of its existence the corpus luteum, as stated, produces a growth substance which affects the uterus. After the first period has passed the existence of

this substance cannot be demonstrated, despite the fact that the uterus maintains its power to react to such a substance in the typical manner ²⁶ (as shown by the effects of an artificially accelerated ovulation).^{16 20} On the other hand, we have seen that the corpus luteum produces throughout a much longer period of its existence a substance which prevents ovulation.¹⁰ Shall we then conclude that the corpus luteum produces two different substances, one determining growth processes in the uterus and the other the inhibition of ovulation, or are we dealing with differences in the quantity in which one and the same substance is produced at different periods of the life of the corpus luteum? In the latter case we would have to make the further assumption that for the growth effects a much larger quantity of this substance is required than for the inhibition of ovulation. This question cannot be definitely answered at the present time, but we must consider it a step forward that the established facts make it possible to put the problem in such a definite manner.

3. CYCLICAL CHANGES IN MENSTRUATING ANIMALS. After the mechanism of the cyclic changes in the uterus had thus been experimentally analyzed in the case of non-menstruating animals, it was of interest to correlate with this cycle the cyclic changes found in the uterus of menstruating animals. The cyclic changes in the uterus of menstruating animals have been studied especially by Heape,²⁹ Marshall³⁰ and Hitschmann and Adler.³¹ Subsequently Robert Meyer,² Ruge,³² Schroeder³³ and others applied the knowledge which the experimental analysis of the sexual cycle in the guinea-pig and rabbit had furnished, especially as to the significance of the corpus luteum, to the study of the sexual cycle in woman, and correlated these cyclic changes with the periods of development and decline of the corpus luteum. A consistent comparison

between these cycles led necessarily to the conclusion that the growth processes in the uterus must be preceded by ovulation and thus the views of L. Fraenkel,^{25 27} who maintained that ovulation preceded menstruation were confirmed. We may then infer that conditions in woman are essentially the same as in the animals in which the mechanism of the sexual cycle had previously been established by experiment. Uterine heat and ovulation and the morphological changes accompanying them depend upon the absence of the corpus luteum, while the decidual changes and phenomena of secretion in the glands, depend upon its presence. Menstruation introduces a complication into the cycle, inasmuch as the cessation of growth processes is followed by necrotic changes in the mucosa and by hemorrhages. These changes are perhaps in some respects analogous to those observed in deciduomata and in tumors; here, also, a cessation of growth processes is followed by hemorrhage and necrosis of the tissues. In the uterine cycle of menstruating animals there is therefore added to the growth phenomena initiated by the corpus luteum and mature follicle a secondary growth process, namely, a regeneration of defects in the uterine mucosa.

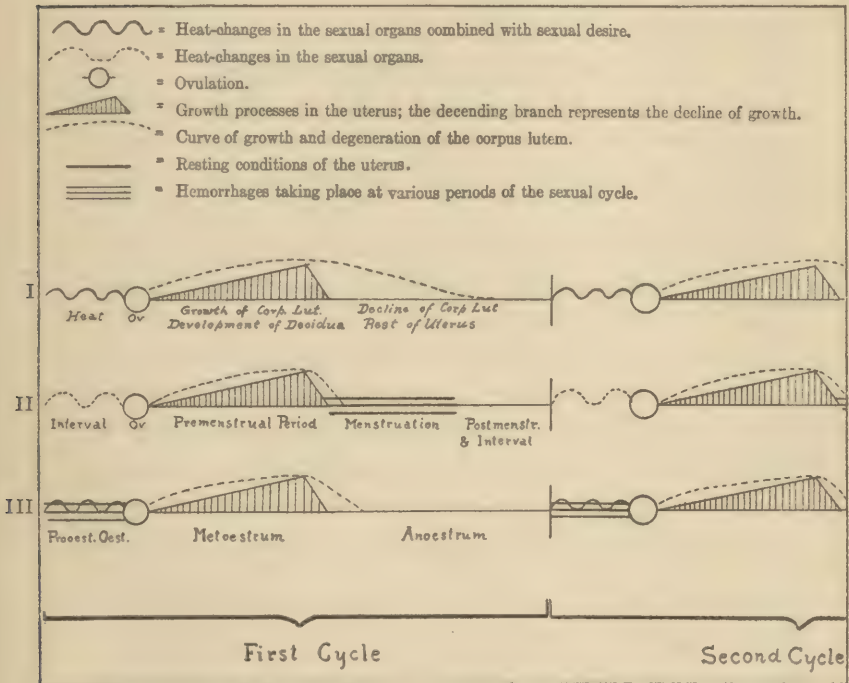
A. VASOMOTOR PHENOMENA IN MENSTRUATION. It is highly probable that vasomotor phenomena play some part in menstruation. These vasomotor phenomena are normally dominated by the ovary and probably by the corpus luteum. Menstruation commonly ceases soon after castration and reappears after transplantation of the ovaries, as Halban³⁴ and others have shown. Observations have, however, been recorded (Gellhorn³⁵ and others) which seem to indicate that menstruation may persist for a long period of time without the presence of ovaries. It is possible that in those cases which were complicated by inflam-

matory processes in the pelvis remnants of ovaries had remained, inasmuch as the complete absence of the ovaries has, as far as we are aware, not been verified by autopsies. But if it is true that menstruation may actually occur permanently without the presence of ovaries and not merely for a brief period following castration, we would have to assume that certain vasomotor phenomena after they have once been initiated by the ovaries may later be called forth through processes in the cerebral nervous system. The fact that hypnotic suggestion can influence the time of the onset of menstruation indicates that the central nervous system does play a certain rôle in menstruation.

B. HEMORRHAGE DURING HEAT. There are certain animals in which the uterine cyclic changes are still wrongly interpreted by some recent workers. I refer particularly to the cycle in the dog. Here slight hemorrhages seem to occur during the period of heat; these hemorrhages have been erroneously analogized with menstruation in primates. The careful work of Keller,³⁶ however, makes it perfectly clear that these hemorrhages are due to the hyperemia which characterize the uterine mucosa at the time of heat and ovulation. True menstruation evidently does not occur in the dog. The cycle in the dog accords therefore in all essentials with what has been established experimentally in the guinea-pig and in the rabbit, and likewise confirmed in the case of woman. It is therefore inadmissible to use such cyclic changes as an argument against the significance of the corpus luteum for menstruation.

V. OTHER NON-CYCLICAL OVARIAN INFLUENCES

1. **TROPHIC.** In addition to the functions which we have discussed so far and which refer to cyclical changes within the ovary and uterus, the ovary exerts a trophic influence of a non-cyclical nature. After extirpation of



Diagrammatic representation of the sexual cycle. I. In the guinea-pig. II. In apes and women. III. In the dog.

the ovaries the uterus becomes markedly atrophic. This effect, however, does not immediately follow castration. Considerable time must elapse before the atrophy becomes very marked. In a similar manner atrophy of the mammary gland follows castration. If the castration takes

place before puberty, neither uterus nor mammary gland become sexually mature. Likewise at the onset of the menopause atrophic conditions in the ovary are accompanied by atrophy of uterus and mammary gland. Through transplantation of the ovaries in animals and man it has been possible to prevent the atrophy of the uterus and mammary gland which follows castration or lack of function of the ovaries. (Morris,³⁷ Knauer,³⁸ Halban,³⁹ Marshall and Jolly,⁴⁰ Martin⁴¹ and others.)

2. EFFECT ON SECONDARY SEXUAL CHARACTERS. The ovary determines the development of secondary sexual characters in the female, and it is even possible through transplantation of the ovaries into castrated males to call forth growth processes in the mammary gland (Steinach,⁴² Athias⁴³), and to change male into female psychological characters.⁴² As Steinach has shown, the ovaries not only stimulate the development of female sexual characters but also inhibit the development of male characters.⁴² On the basis of the effect of transplantation of the ovaries we may conclude that the ovaries exert this influence through a substance given off into the circulation. This substance then acts on the uterus and mammary glands and other organs either directly or through the nervous system. Which part of the ovaries exerts this function it is impossible to state at present with any degree of certainty. Steinach believes, it seems to me without sufficient foundation, that the interstitial gland is responsible for this effect. Pearl, who described in a cow the change from certain female into male characters, believes that the absence of a substance secreted by the corpus luteum was responsible for this change, because the cystic ovaries of the animal contained all ovarian constituents with exception of the corpus luteum.⁴⁴

In more recent experiments Pearl ⁴⁵ succeeded in diminishing in female fowl the retardation in growth characteristic of the female sex by adding Ca salts to the diet; corpus luteum substance or extracts of corpus luteum in NaCl solution counteracted the effect of the Ca salts and thus tended to preserve the female differential characters. Pearl concludes therefore that the corpus luteum is responsible for the production of secondary sexual characters. And inasmuch as corpus luteum is not present in fowl, he furthermore concludes that an identical substance must be produced also in other parts of ovary. If this assumption should prove correct, it then would follow that there are several active substances in the corpus luteum, because the substances through which the corpus luteum affects the cyclic changes in the uterus and which regulate ovulation, are not present in the rest of the ovary but only in the corpora lutea, and the substance responsible for the cyclic changes in the uterus appears only at certain periods in the life of the corpus luteum. At best we can therefore assume on the basis of Pearl's interesting experiments that certain substances present in the corpus luteum are not specific, but common to both the corpus luteum and the rest of the ovary. It would be very desirable to carry on control experiments in which ovarian instead of corpus luteum substance were used in similar experiments.

VI. EFFECTS PRODUCED BY OVARIAN EXTRACTS

Attempts have been made to throw additional light on the character of the active substances in the ovaries by injecting extracts or press juices of constituents of the ovaries or other organs into virgin or castrated animals. We found that the repeated inoculation of the corpus luteum of the guinea-pig at a time when it was known to contain the active growth substance, into other guinea-pigs, did not have the effect of the living corpus luteum which is secreted continuously within the organism. It is, however, possible that it exerted a slight effect in one or two cases. R. T. Frank ⁴⁷ found that injection of corpus luteum substance obtained from other species was without

effect on the cyclic changes of the uterus and did not permit the production of deciduomata. In more recent experiments we found that injection of cow corpus luteum extracts in NaCl solution does not prevent necrosis of the deciduomata nor does it prolong the life of deciduomata in guinea-pigs.¹⁸ On the other hand, recent experiments by Aschner,⁴⁸ Adler,⁴⁹ Fellner,⁵⁰ Schickele,⁵¹ Okintschitz,⁵² seem to establish the fact that injection of extracts or press juices of ovaries and placenta, cause hyperemia of conjunctiva and vulva, and hyperemia and thickening of the uterus. The epithelium of the uterus becomes higher and the connective tissue cells of the mucosa vesicular. In estimating the significance of this latter work we must emphasize (1) that the results of various investigators are contradictory as to the active constituent in the ovary; while some find the corpus luteum effective, the majority find it inactive or at least less active than other parts of the ovary. There are also discrepancies as to the effect of boiling and the effect of the medium of extraction on the efficacy of the extract. (2) It has been erroneously assumed by some investigators that cyclic growth processes in the uterus have been imitated through the injection of these substances. On the contrary it seems that the typical effects which the corpus luteum exerts in the living state have in no case been reproduced in these experiments. On the other hand, they seem to establish the fact that circulatory effects and a turgescient condition of the uterus can be produced through injection of these substances and that the atrophy of the uterus following castration probably can be avoided. (3) It is uncertain how far the results obtained with extracts of generative organs are specific for these extracts. Sufficient control experiments with other organs are as yet lacking. It seems, however, that thymus extract acts similarly to extracts of generative organs.⁵⁰

These experiments can at best supplement results

obtained by means of better methods, but it is inadmissible on the basis of such experiments to invalidate conclusions which rest on an experimentally secure foundation.

VII. FERMENTS IN THE OVARY AND UTERUS

A few authors investigated certain chemical actions of uterus and ovaries *in vitro*, in order to throw light on the character of the substances given off by the ovary and transmitted to the uterus. Thus Halban and Frankl⁵³ and Aschner⁵⁴ found the uterine mucosa to contain a tryptic ferment which was apparently present in increased quantity during the premenstrual period. Halban assumes that this tryptic ferment is responsible for the decidual transformation of the uterine mucosa. It is, however, apparent that this investigator did not obtain the proliferative changes characteristic of true decidua, but obtained merely a non-specific swelling of cells, such as alkali and trypsin produce in gelatin. R. T. Frank⁵⁵ showed in a very careful investigation that erepsin as well as amylase and lipase are present in the placenta. Schickele⁵¹ found in the ovary and in the uterine mucosa substances which inhibit coagulation of blood and produce hyperemia. He believes that these substances originate in the ovary, are transmitted to the uterus, and are responsible for the menstrual bleeding. While it is very probable that these substances play an important part in the menstrual hemorrhage, it is very unlikely that they originate in the ovary and are merely given off to the uterus.

In conjunction with Moyer S. Fleisher, we found that the uterine mucosa and ovary of the guinea-pig exerts the strongest fibrinolytic power of any organ in the body which we examined.⁵⁶ The uterus of the rabbit also exerts a strong fibrinolytic power. The ovary of the rabbit, on the other hand, is devoid of this power. We may

therefore conclude that the fibrinolytic power of the uterus is not derived from the ovary but originates independently in the uterine mucosa. It is very probable that the fibrinolytic and coagulation inhibiting substances are identical and that they are of importance in menstrual bleeding, but it is quite evident that these substances are not identical with the substances sent from the ovaries to the uterus which are responsible for the cyclic changes in the uterus and for the prevention of its atrophy.

VIII. INFLUENCE OF THE OVARY ON THE MAMMARY GLAND

1. TROPHIC. The relation between ovary and mammary gland is as yet incompletely analyzed. We know that, when castration is performed at an early period of life, the mammary gland remains undeveloped and that it atrophies if castration is practised at a later period in life. If ovaries are transplanted into young male guinea-pigs the mammary gland begins to develop, to form acini and even to secrete milk (Steinach,⁴² Athias⁴³). It is not definitely known at the present time which part of the ovary is responsible for this effect. Steinach, it seems to me, on insufficient evidence, assumes that the interstitial gland is responsible for this effect. Athias found that in such male guinea-pigs into which ovaries had been transplanted and the mammary gland had grown, corpora lutea were absent in the transplanted ovaries. He assumes, therefore, that either the follicles or interstitial gland caused the proliferation.

2. CYCLICAL. Ancel and Bouin,⁵⁷ as well as R. T. Frank and Unger,⁵⁸ found in the rabbit a growth of the mammary gland concomitant with the development and growth of the periodic corpus luteum; and they are inclined to attribute this growth to the activity of the corpus luteum. During pregnancy this growth is followed

by the production of milk. This secretory action is attributed by Hildebrandt⁵⁹ and others to cessation of the growth stimulus; by Ancel and Bouin,⁶⁰ though apparently without sufficient basis, to a so-called myometric gland which is found in the uterus during pregnancy, or after experimental production of deciduomata.

In conjunction with Cora Hesselberg, we were able to show⁶¹ that in the guinea-pig the cycle of the mammary glands consists of two phases analogous to the phases of the uterine cycle. The first phase, comprising the period of heat and the several days following ovulation, shows mitotic cell proliferation of the gland. This first phase depends upon the absence of the corpus luteum, but upon the presence of another constituent of the ovaries. This phase can be accelerated through early excision of the corpora lutea. The second phase, corresponding to the growth and activity of the corpus luteum, is not accompanied by proliferation of the gland; only toward the latter part of this period proliferation is resumed and becomes especially frequent in cases in which simultaneously well preserved deciduomata and corpora lutea are present. During pregnancy mitotic proliferation of the g. appears only a little earlier than during the ordinary cycle unaccompanied by pregnancy. Experimentally accelerated ovulation during pregnancy is again accompanied by proliferation of the mammary gland. We may then assume that in certain respects the mammary gland of the guinea-pig requires a stronger proliferative stimulus than the mammary gland of the rabbit. The relation between functions of corpus luteum and mammary gland is apparently not as simple as could have been assumed on the basis of observations in the case of the rabbit alone, especially if we consider with how great a regularity the mammary gland shows some proliferation in the guinea-pig at the time of ovulation. During pregnancy the prolifera-

tion of the mammary gland is, at least in the guinea-pig, much greater than during the ordinary sexual cycle.

The cause of the proliferation during pregnancy is not definitely established. Lane-Claypon and Starling⁶² sought the substances causing proliferation and milk secretion in the embryonic tissues in the rabbit. R. T. Frank and Unger⁵⁸ showed that this effect of fetal extracts is not regular in the rabbit and is absent in the rat. Other investigators (Aschner and Grigoriu,⁶³ Fellner⁵⁰) obtained proliferation of the mammary gland through extracts of placenta and ovaries, but corpus luteum extract proved ineffective in the hands of Aschner and Grigoriu.

We found¹⁸ in the guinea-pig aqueous corpus luteum extract without effect on the mammary gland, while according to recent not yet published experiments, R. T. Frank found that in rabbits the lipoid bearing fractions of extracts of both placenta and corpus luteum were effective in producing proliferation of the mammary gland, while in the rat both were ineffective. The rat seems therefore to behave toward extracts in a way similar to the guinea-pig, while the mammary gland of the rabbit seems to be much more responsive to the effect of extracts.

At the present time the mechanism underlying the cyclic changes in the mammary gland can be considered only as partly analyzed.

3. CANCER OF THE BREAST. Quite recently we found⁶⁴ that the ovaries are of importance for the growth processes in the mammary gland in still another way. The function of the ovaries is to a great extent responsible for the development of cancer in the mammary gland in mice. If we castrate female mice at a time when they have already entered into the period of sexual maturity, the incidence of cancer of the breast, which is by far the most frequent cancer in mice, in strains with a hereditarily determined high tumor rate, is reduced from approximately 60 per

cent. or 70 per cent. to 9 per cent. We may attribute this effect of castration to the elimination of the cyclic growth stimuli which emanate from the ovaries and act on the mammary gland in the normal animal. It is uncertain which constituent of the ovary is responsible for this effect.

As we have shown, the relations between ovaries and uterus are complex. Transitory organs like the corpus luteum and placenta enter into the play of mechanisms. It is now possible to separate experimentally the effect of the maternal and embryonal part of the placenta in these complex phenomena. Therefore, a beginning in this direction has already been made. It will be necessary eventually to complete this analysis. In addition we must consider the possibility that the relation between uterus and ovaries represents a chain of connected phenomena, of which the first and last members are uterus and ovaries, the intermediate links being formed by other glands of internal secretion or certain nervous structures. An analysis of these latter relationships, however, is outside the realm of the problems to be dealt with in our report.

SUMMARY

Without attempting to present a complete summary of this paper, the following most important conclusions may be specially emphasized:

1. The ovary is a complex gland of which the most important constituents are follicles in various stages of growth and atresia, and corpora lutea. In addition we find in some species interstitial gland and sometimes embryonic structures developing parthenogenetically from eggs.

2. Cyclical changes occur both in the ovary and secondarily in the uterus and mammary gland.

3. The primary cyclical changes in the ovary are in sequence: follicle ripening, ovulation, corpus luteum

formation. In some species ovulation is accompanied by degeneration of all but the smallest follicles.

4. An elaborate self-regulating mechanism controls ovulation. Normally the corpus luteum inhibits ovulation. During pregnancy the life of the corpus luteum is prolonged. Experimentally ovulation can be influenced at will, accelerated by excising all corpora lutea, or retarded by producing artificial deciduomata. The retarding action of the corpus luteum is chemical, not mechanical.

5. The corpus luteum has a sensitizing action upon the uterus. This action can be analyzed by experimental methods. If the uterus is incised or mechanically stimulated at the time during which the corpus luteum is elaborating this growth substance, maternal placenta (deciduoma) is formed. The mechanical stimuli, therefore, assume in this respect the function which the ovum exerts under normal conditions. The form of growth response of each species is characteristic. The localization of sensitization varies in different species being limited to the uterus in rabbits and guinea-pigs, but distributed more widely in the human female. No specificity exists in the sensitizing substance given off by the corpus luteum as far as different individuals of the same species are concerned. The life period of experimental deciduomata is short except in pregnancy, during which their persistence is prolonged.

6. Corresponding to and dependent upon the cyclical ovarian changes, uterine cyclical changes occur. The cycle consists of heat, growth with associated glandular activity, regression and interval. Heat probably is due to maturation of the follicles and dependent upon the absence of the corpora lutea; growth activity is the result of corpus luteum secretion; regression marks the cessation of corpus luteum secretion, which is followed in the interval by a condition of rest. Pregnancy causing a persistence of the

corpus luteum is characterized by an accentuation but not a prolongation of the active phase, and an inhibition of the uterine cyclical changes throughout gestation.

7. While it is possible to produce, experimentally, during pregnancy a new ovarian cycle, through excision of the corpora lutea, such a new ovarian cycle is not followed by a new uterine cycle. During pregnancy a mechanism is at work preventing the uterine mucosa from responding to the stimuli given off by various ovarian structures.

8. It follows from 4 and 5 and 6 that the corpus luteum subserves at least two functions, inhibiting ovulation and producing a substance which causes growth in the uterus.

9. The ovary shows other non-cyclical functions. It has a trophic influence on the genitals and either primarily or secondarily determines the development of the secondary sexual characters.

10. The ovary, likewise, controls the development of the mammary gland. It exerts a trophic influence on this organ and determines its normal cycle. During heat and subsequent to ovulation proliferative changes occur; these cease while the corpus luteum develops and functionates.

11. The incidence of breast cancer in mice is greatly reduced by castration.

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TRANSPLANTATION AND RETENTION OF OVARIAN TISSUE AFTER HYSTERECTOMY

BY WILLIAM P. GRAVES, M. D.
Boston, Mass.

THE purpose of this paper is to inquire primarily into the influence of ovarian tissue retained in the body after hysterectomy on the so-called ablation symptoms. In making such an inquiry we must clearly define the nature of ablation symptoms and consider what theoretical knowledge we have of their causation. We must determine from experimental and clinical evidence the anatomical fate of retained ovarian tissue and must observe whether or not important changes take place in the physiological action of such tissue. From clinical statistics we must discover whether or not the retention of ovaries has a beneficial or preventive influence on ablation symptoms. In like manner it is necessary to learn whether the anatomical and physiological changes in retained ovaries may not be productive of pathological conditions capable of serious harm to the patient. Finally we must weigh the evidence of possible good and possible harm from ovarian retention.

I. ABLATION SYMPTOMS

Ablation symptoms may be classified as historic, traditional and modern. By historic is meant that distressing symptom-complex which in the earlier days of surgery fol-

lowed a considerable proportion of castration operations, consisting of intense flushings, sweatings, palpitation, headaches, extreme and protracted weakness, sleeplessness and many other similar disturbances, that persisted sometimes for many years. In addition to these vasomotor changes, there were often associated hysterical and psychoneurotic manifestations that occasionally led to mental disorders of a still graver nature. Thanks to improved surgery serious sequelæ like the foregoing are nowadays rarely encountered, for it has been shown that the more distressing symptoms of the artificial menopause are for the most part excited by disabling and discouraging postoperative complications, which were formerly of common occurrence after hysterectomy.

The traditional ablation symptoms relate to those physical changes which in the popular mind are supposed to take place after removal of the ovaries. Chief among these are an abnormal accumulation of fat, inevitable sexual insensibility and a general acquisition of masculine characteristics, such as roughening and deepening of the voice, coarsening of the features and growth of facial hair. These need only to be mentioned as an unfounded belief deeply ingrained in the lay mind, having its origin doubtless in a vague analogy to the changes produced by castration of unmaturing animals.

The term modern ablation symptoms relates to the comparatively mild vasomotor disturbances that ensue after the extirpation of the uterus and adnexa by improved surgical technic.

In our use of the term ablation symptoms we shall refer for the most part to hot flushes, for they alone are sufficiently distinctive for accurate statistical observation. There are, to be sure, certain other post-hysterectomy manifestations, sometimes observed independent of, but usually associated with flushes, the most important of which are

sensations of alternate heat and cold, palpitation, feelings of anxiety, dizziness and sleeplessness. They are, however, extremely inconstant. They are common enough among women without pelvic lesions and are not infrequently seen after any surgical operation not involving the genital organs. They can therefore hardly be regarded as unequivocal ablation symptoms, in the same sense as hot flushes, the appearance of which is entirely and specifically characteristic.

Regarding the etiology of ablation symptoms it must be admitted that our knowledge is little more than theoretical. Walthard has interestingly ascribed them to a psychoneurosis, resulting from overvaluation of minor discomforts. Such a state of mind he describes as a pathological mental habit. The condition is greatly exaggerated if there be an associated psychic distress as from self-depreciation on account of the loss of reproductive organs, or from marital difficulties caused by the patient's pelvic condition. Walthard shows how psychic pain may set up subcortical reflexes in various organs of the body, for example, in the muscular and digestive systems. By analogy he argues that such reflexes may set up functional disturbances in the glands of internal secretion with consequent changes like those of ablation symptoms. Cannon's work on the effect of the emotions on the secretions of the adrenal gland and sympathetic systems is a striking substantiation of this theory. Walthard describes as "psycho-secretory" such effects of the mind on the glands of internal secretion.

Although we cannot wholly accept Walthard's theory that ablation symptoms are psychoneurotic in origin, nevertheless, we can scarcely deny that his ideas offer a partial solution of the problem. On the basis of this theory it is easier to explain the fact that as a rule ablation symptoms are greatly intensified by discouraging post-operative complications or by mental distress, such as that over the loss of organs, and that such symptoms may often

be made to disappear at once, on relieving the patient of her physical or mental disability.

Walthard's theory, however, cannot be accepted in toto for unequivocal ablation symptoms are often observed in patients, whose physical ills have otherwise been completely relieved by the operation and to whom the removal of the genital organs is a matter of great mental satisfaction.

Schickele has attempted to explain ablation symptoms on the ground that the elimination of the ovarian secretion, which is vaso depressor in its action, allows a gradual and prolonged rise in the blood tension and that vasomotor symptoms result from this increase of pressure. He also showed that the blood tension may be reduced by the administration of ovarian extract. It was found, however, that ablation symptoms and rise in blood pressure do not always run parallel, that is to say, each may occur independently of the other. Schickele explains this irregularity on the basis of individual differences in patients, especially with reference to the excitability of the sympathetic nervous system. He makes no attempt to explain the fact that ablation symptoms usually come on very soon after the operation, while the rise in blood pressure does not appear before several weeks.

Schickele encounters another difficulty in his observation that "when one or both ovaries are left in loco after hysterectomy, the vasomotor symptom-complex happens *just as often* as when the ovaries have been extirpated." These symptoms, he says, are extraordinarily similar to, if not exactly like, ablation changes. He names them "retention symptoms" and ascribes them to products of ovarian secretion which, not having a uterine outlet collect in the body and cause the characteristic disturbances.

Schickele's theory, though suggestive is nevertheless unsatisfactory, for it is difficult not to believe after comparing cases exhibiting ablation and retention symptoms, that the symptom-complex in both cases is not only similar but identical and originates from the same cause. If this

be true, how then can we reconcile the fact that the same complex may be produced either by removal or retention of one and the same organ.

In order to arrive at an answer to this question it must be borne in mind that the ovary is an integral part of two physiological systems, namely, the secretory and reproductive, between which it occupies, so to speak, the position of a connecting link. On the one hand, the ovary is a member of the correlated chain of glands of internal secretion, the integrity of each one of which is necessary for the proper physiological balance of the whole group. During the period of development before puberty, the interrelation between the ovary and the other glands is of great importance; during maturity up to the time of the menopause the ovary plays a subordinate but by no means an insignificant rôle. On the other hand, in the reproductive system the ovary is the predominant factor, but it is not an independent factor, for its proper function depends on its physiological association with the uterus and endometrium. Disturbances in either the secretory or reproductive system create reactive changes in the other. Familiar examples are the menstrual abnormalities attendant upon diseases of the pituitary, thyroid and adrenal glands, while the reverse action is seen in the anatomical changes of the same glands during pregnancy and their various constitutional manifestations often seen with dysmenorrhea, myopathies, and other pelvic diseases.

Inasmuch as the normal function of the ovary is dependent on its physiological connection with the uterus, a disturbance or severance of this connection supposedly produces an ovarian dysfunction, which, in turn is likely to upset the balance of the other ductless glands, thus creating in them a corresponding dysfunction. Hence the evidences of hypersecretion of the thyroid and adrenals, for example, in certain cases of dysmenorrhea. Thus, too, a disturbance

of the ovarian function from removal of the ovaries from the body with or without the uterus, or from retention of the ovaries in the body without their uterine complement, is likely to be communicated to the other secretory glands with corresponding dysfunctional symptoms. In this way, then, both ablation and retention symptoms, as well as those similar changes that appear in the course of various pelvic diseases, are ascribed to reactive influences in glands other than the ovaries. The terms ablation and retention symptoms are therefore inadequate and misleading. One would more correctly refer to the general complex as dysfunctional symptoms and to specific cases as dysfunctional ablation or dysfunctional retention symptoms.*

The vasomotor nature of the symptom-complex is due to the fact that the secretory reaction is exerted chiefly on the sympathetic nervous system. The irregularity of the appearance of the symptoms is explained by individual variation in the power of adaptation to changes in the secretory system. Inasmuch as the ultimate effect is on the sympathetic nerves it is to be expected that in patients with a nervous predisposition, or when postoperative complications, or mental distress increase the nervous irritability, the dysfunctional symptoms would be exaggerated and prolonged. Such we have seen to be the case.

That the majority of patients suffer comparatively slight inconvenience from the removal of the ovaries, and many of them none at all, is evidence of the subordinate part played by the ovary during maturity in the group of ductless glands.

The foregoing theory of the origin of ablation symptoms explains the apparently anomalous cases in which the

* The term "*dysfunction*" is employed throughout this article without implying any change in the chemical nature of the secretion. similarly the word "*changed*" secretion refers to a disturbed or abnormal effect, irrespective of the cause of its production.

symptom-complex is made completely to disappear by the *removal* of the ovaries. In such cases there exists a disharmony in the uteroövarian function which causes reactive disturbances in the internal secretory apparatus. Extirpation of the uterus and ovaries removes the source of irritation and the glandular system resumes its normal balance. The following case illustrates this point extremely well:

A young woman of 23, single, consulted me for continuous and troublesome hot flushes, which were especially severe and associated with other nervous and vague discomforts at periods averaging about five or six weeks. She had never menstruated. Examination showed a complete absence of the vagina. No internal genital organs could be felt in the pelvis per rectum. The patient was told that she probably had some ovarian tissue which by being unable to functionate properly was causing the trouble. An exploratory laparotomy was advised.

On opening the abdomen two entirely normal ovaries were discovered, each one at about the level of the lower pole of the corresponding kidney. In one ovary was a well-formed corpus luteum. Connected with each ovary was a tube and rudimentary strand of solid uterine tissue, forming a complete uterus didelphys with entire absence of the vagina. Ovaries and rudimentary uterus were removed. The operation was followed by an almost complete disappearance of hot flushes and with consequent improvement in general health and nerve control.

In this case the disharmony consisted in the association of a rudimentary uterus with fully developed ovaries so that normal function was impossible. The result was typical dysfunctional symptoms of the same nature and origin as those seen from ovarian retention after hysterectomy.

The following case also illustrates the restoration of normal secretory function by hysterectomy and removal of the ovaries:

A. T.; age 45; two children; one miscarriage with twins. Seen January 16, 1915. Chief complaint: severe menorrhagia, insomnia, hot flushes, general nervousness. Examination: Uterus in position, normal contour, slightly larger than normal. Operation January 19, 1915: Supravaginal hysterectomy with the removal of ovaries. Pathological examination of uterus and ovaries entirely negative. Hot flushes disappeared immediately after operation and did not recur. Completely regained nervous control.

In this case the dysfunctional secretory activity was evidently the result of a disharmony of function between ovary and uterus as shown by severe menorrhagia without anatomical lesion. The patient was cured by removal of both uterus and ovaries.

The theory that ablation symptoms are due to dysfunctional activity in the internal secretory apparatus has some support from experimental evidence though it has as yet not been indisputably proved. Cristofolletti and Adler produced by subcutaneous injections of small doses of adrenalin, symptoms similar to those of the menopause, *i. e.*, rise in blood tension, irregular pulse, blushing of the skin, headaches and feelings of anxiety. Adler found a greater reaction to adrenalin in individuals from whom the ovaries had been taken. Results of this kind are suggestive but by no means conclusive, for none of the symptoms produced can be said to be specifically of the menopause type.

To the gynecologist the practical point in the study of ablation symptoms is the question of the removal or retention of ovarian tissue in the course of hysterectomy operations. Theoretically we have attempted to show that the symptom-complex results from a breaking of the harmony of the uteroövarian function. Upon this theory it is reasonable to expect that if the uterus be extirpated, dysfunc-

tional symptoms would ensue whether the ovaries be removed or not. Let us now see whether or not this conclusion is borne out by clinical evidence.

II. POSTOPERATIVE RESULTS FOLLOWING HYSTERECTOMY WITH ONE OR BOTH OVARIES LEFT IN SITU

It is of course obvious that the leaving of ovaries in the pelvis after hysterectomy is feasible only in a limited number of cases. It is, for example, out of the question after operations for malignancy or extensive tuberculosis of the pelvic organs. In cases of a pelvic inflammatory disease which is sufficiently destructive to require hysterectomy the ovaries should not be allowed to remain, even if there be considerable normal ovarian tissue, for in these cases the surface epithelium has invariably been damaged to such an extent by adhesions that the organ is sure to become adherent again. An isolated ovary buried in adhesions is extremely liable to form retention cysts which may cause so much trouble to the patient as to require removal later. The operation of digging out an adherent cystic ovary from the depths of a pelvis in which hysterectomy has been done is a difficult and serious one. The following case illustrates the inadvisability of ovarian retention in cases of hysterectomy for pelvic inflammation:

N. D.; age 24. Case of chronic pelvic inflammation. Had had a previous conservative operation. Operation: Supravaginal hysterectomy—removal of left adnexa. Right ovary which was undamaged left in situ. Patient returned one year later with small postoperative hernia, painful cystic tumor in pelvis, and suffering from severe hot flushes. Operation: Cyst of ovary densely adherent in pelvis, removed with much difficulty on account of bleeding. Hernia repaired. Good recovery. Great improvement in hot flushes following operation.

Leaving in one or both ovaries is anatomically feasible in certain cases of small or moderate-sized myonata, or in

the myopathies without apparent lesion, or in procidentia cases in which the method of removing the uterine body is adopted. Even under these favorable conditions it is probable that the surface of the ovary usually becomes adherent. The germinal epithelium is a very delicate structure and readily desquamates under comparatively slight inflammatory or circulatory influences. It is for this reason that the ovary has such a marked disposition to adherence to neighboring organs.

I have frequently had occasion to remove ovaries that had been retained at a previous hysterectomy operation and in every instance the ovaries have been found densely adherent, degenerated and cystic.

In addition to the tendency which the retained ovary has to form adhesions and cysts it also possesses the power of developing tumors which may be of a malignant nature. Experimental evidence demonstrates that if the ovary be left *in situ* with due care to preserve its blood supply it may continue to ovulate for a considerable period. In the course of time the functional activities cease. It must, however, not be inferred that the retained atrophied ovary loses its power of abnormal cell proliferation any more than does the atrophied ovary of the menopause. The following case illustrates the malignant fate of a retained ovary nine years after a hysterectomy for fibroids:

R. S.; age 47. Had had operation nine years before. Removal of uterus for fibroid, both ovaries being left *in situ*. Examination showed large adherent tumor in pelvis. Operation, October 3, 1916: Removal of large papillary cyst of right ovary very adherent to the intestines. Intestinal wall injured and repaired. Left ovary, adherent, small and shrivelled, removed with atrophied tube. Pathological examination: Malignant papillary cystadenoma of right ovary. Left ovary atrophied, but germinal epithelium very prominent and active, dipping down into stroma and showing a papillary inclination.

Evidently early stage of cystadenoma. Patient made good recovery from ether, but a few weeks after discharge showed irregular masses in pelvis, probably recurrence of malignant disease.

I am indebted for the following case to Dr. Hugh Williams, who consulted me during its progress:

M. B.; age 25. Two children, two miscarriages. Last pregnancy four years previous. Chief complaint: Menorrhagia and metrorrhagia, for which curetting two years before had given only temporary relief. Operation August 30, 1910. Vaginal hysterectomy. Both ovaries and tubes left *in situ*. Pathological report: Sclerotic uterus with atrophied mucosa. Normal convalescence. Following operation severe menopause symptoms. Every twenty-eight days distressing menses with menstruation with severe pelvic pain, headache and nausea. At these periods psychoneuroses appeared which gradually grew worse until they appeared in the form of insane outbursts each month. Retained ovaries painful and tender.

January 8, 1913, abdominal operation. Removal of both tubes, ovaries and appendix. Pathological report: Ovaries cystic, fibrous, corpora hemorrhagica. Normal convalescence.

Later history. Patient recovered immediately and completely from menopause and psychoneurotic symptoms. Is now perfectly well.

In this case the retained ovaries not only underwent anatomical changes that caused pain and tenderness, but they also produced dysfunctional vasomotor and psychoneurotic symptoms of the most pronounced hysteric type. They were made completely to disappear by removal of the ovaries.

From the above cases it is sufficiently evident that an ovary retained *in situ* is by no means a harmless organ, and that its retention may subject the patient to later trouble of a serious kind.

So far we have considered the retained ovary in relation to its anatomical possibilities. We will now regard it from a physiological viewpoint.

It is an extremely widespread belief among surgeons that the retention of ovaries *in situ*, after removal of the uterus, eliminates partially or completely the so-called ablation symptoms. At a meeting of the American Gynecological Society in 1910 at which the subject was fully discussed there was but one dissenting voice to the recommendation by the readers of papers for conservation of ovaries after hysterectomy. Definite statistics on the comparative merits of conservation and ablation with special reference to symptoms of the surgical menopause are somewhat meager; nevertheless, what testimony we have in the literature is very significant. Schickele finds "that when one or both ovaries are retained the vasomotor symptom-complex happens *just as often* as when the ovaries have been extirpated."

Walthard in a comparison of his own cases finds an improvement of only 2 per cent. in retention over ablation.

Walthard again in a later article sums up the statistics collected by Sarwey, of Tübingen, Cemach, of München, and Senn, of Berne, and finds that "in those patients whose uterus and ovaries have been removed, only in from 1 to 2 per cent. of all cases do the above mentioned symptoms appear more commonly than in those whose ovaries have been left behind."

Konstantinidis in 134 cases of hysterectomy with retention of one or both ovaries found that one-half suffered from vasomotor, one-third from trophic and one-seventh from psychic disturbances.

My own figures are given in the table below in which a small number of retention cases is compared with a much larger number of total ablation cases with special reference to hot flushes. In this series the retention cases actually suffer by comparison as far as severity is concerned though the incidence of symptoms is almost identical in the two series.

Walthard and Schickele both find that the symptoms appear in approximately 80 per cent. of all hysterectomy cases, whether ovaries are retained or not. It will be seen that my results correspond closely to their figures.

In contrast to these figures are those of Dickinson, who in a series of 163 cases in which ovaries had been retained, reports that "80 per cent. were *free* from the disturbances of the surgical menopause." These figures are not only far ahead of any others that have been published but they are even better than those of the natural menopause, in which it is generally accepted, that about one-half of all women experience vasomotor changes.

Notwithstanding the findings of Dickinson my experience impels me to the conclusion that the retention of ovaries after hysterectomy insures only a slight improvement in the menopause symptoms over ablation, and that this slight advantage, even if it exists at all, does not compensate for the dangers of adhesions with cyst formation, malignant degeneration, and physiological disturbances which the conservation of the ovaries entails.

III. TRANSPLANTATION AFTER HYSTERECTOMY

On account of the prevailing superstition regarding the dire effects of removing ovaries, it is not infrequently necessary for the mental comfort of the patient to leave behind ovarian tissue even though the patient be warned that the retained ovary may cause later trouble. In order to meet this contingency and at the same time to avoid the dangers of leaving ovaries *in situ* the expedient was adopted of transplanting a section of healthy ovary. In the first cases the transplantations were made within the leaves of the broad ligament in the paracervical cellular tissue. This maneuver soon proved unsatisfactory, for in 3 cases the transplanted tissue became cystic and painful. In one of these, menstrual molimina appeared with profuse

nosebleed, which the physician who reported the case to me, regarded as vicarious menstruation. None of the cases were operated on for removal of the transplanted ovary, although in one instance the operation was advised. In the light of these results, the transplantations were then made in the abdominal rectus muscle, from which location the ovary might easily be extracted in the event of troublesome complications. In order to determine the possible influence of transplanted ovarian tissue on the menopause symptoms after extirpation of the uterus letters were written to each patient containing questions as to improvement in health from the operation, presence or absence of hot flushes following the operation, whether they were few or many, diminution of sexual sensibility, and any special increase of general nervousness. The results of this inquiry are partly recorded in the table below in which it will be seen that the showing is actually not so good as in the cases where total ablation was performed. Making allowances for the discrepancy in the number of cases observed and for variations in patients' answers to questions, the conclusion is inevitable that when the uterus has been extirpated transplanted ovarian tissue probably *has no marked influence one way or the other* on the surgical menopause symptoms. This conclusion has also been reached by Tuffier.

Chalfant has recorded 17 cases of transplantation after hysterectomy, the percentages of symptoms in which are appended in the table below. His results in this respect are strikingly similar to mine, excepting that he finds an improvement over his 40 total ablation cases.

Our experience with transplantation lends still further support to the theory that the so-called ablation symptoms are due to a breaking of the uteroövarian harmony, and that if the uterus is removed the retention of ovarian tissue either *in situ* or by transplantation is of little physiological value.

It must, however, be borne in mind that if *the uterus is not removed* the uteroövarian harmony may be retained for a time at least by transplanted ovarian tissue, so that menstruation may continue and ablation symptoms be prevented. This has been proved a number of times, but it is difficult to imagine under just what circumstances it would be advisable to leave the uterus by itself in the pelvis, and transplant the ovaries to some distant part. Our experience has led us very definitely to the conclusion that when both ovaries must be removed, the uterus also should be extirpated, for an isolated uterus almost invariably causes trouble and frequently requires removal. Implantation of the ovaries does not in any way obviate this difficulty, even though it may preserve menstruation for the limited period during which the ovarian graft retains its function of ovulation. The following case illustrates this point:

A. G.; age 30. First seen June 15, 1914. Appendectomy nine years before. Six months before had had "ovaries removed," details of operation not known. Subsequent developments showed that tubes and ovaries had been removed and ovarian tissue transplanted in abdominal fat on each side of median wound. *Menstruation had come on three weeks after operation and had appeared regularly since.*

Chief complaint: Continual pelvic pain. Lump in abdomen. Examination: Small uterus attached to abdominal wall. Adherent tender mass in left pelvis. Movable tender tumor in abdominal wall to left of scar.

Operation June 17, 1914: Hysterectomy. Lysis of omental and intestinal adhesions in right pelvis. Removal of cystic ovarian tissue from fat on left of abdominal scar.

July 27, 1914. Readmitted to hospital. Tumor had appeared in abdominal wall on *right* of incision one week after leaving hospital. Operation: Removal of cystic ovarian tissue from fat on right of median scar.

December 9, 1915. Readmitted to hospital. Tender tumor of abdominal wall on left of incision, which had appeared six months before. Operation: Removal of cystic ovarian tissue in fat on left of scar.

In this case ovarian tissue seemed to be scattered through the abdominal fat and was indistinguishable until it had become cystic.

It has been found possible to restore the uteroövarian harmony, by heteroplastic transplantation in castrated women in whom the uterus has been left behind, so that menstruation is resumed and ablation symptoms made to disappear. Operations of this kind are not universally successful, as heteroplastic grafts do not always take on account of the physiological antagonism of blood and tissue that exists between different individuals.

As has been said above, castration without extirpation of the uterus is an ill-advised operation, and besides other discomforts is apt to be followed by historic menopause symptoms of the severest type. One not infrequently encounters patients who have received surgical treatment of this kind and for a certain number of such cases hetero-transplantation undoubtedly has a field of usefulness.

Notwithstanding the negative conclusions at which we have arrived as to the physiological value of retained ovarian tissue after removal of the uterus, it is nevertheless necessary at times from sentimental reasons to conserve the ovary. In such a case is it better to leave one or both ovaries *in situ* or to transplant? Animal experimentation has shown that an ovary retained in place with careful consideration as to its blood supply retains its anatomical functions much longer than does one that has been grafted (Kawasoye). So far as the secretory influence on the general organism is concerned the statistics presented in this paper seem to show an apparent advantage in favor of the ovary retained *in situ*. It is, however, the custom of the writer, when conservation is imperative to forego this somewhat doubtful advantage and instead to graft a section of the ovary in the abdominal wall where its removal if necessary will be a simple procedure and not a serious

major operation. It is done with the full conviction that the only possible benefit it can have is to relieve the mental distress of a patient whose mind cannot be disimbuied of an ill-founded superstition.

IV. STATISTICS

The appended table is the result of an investigation to determine the incidence and gravity of ablation symptoms. As stated above, hot flushes were taken as the standard, for they are far more constant than other vasomotor symptoms, and are nearly always present if other symptoms occur. The number of cases of retained ovaries is too small for complete comparison. As there were only 10 personal cases to record, 16 of other operators were taken from the hospital records in order to make the list more valuable. Notwithstanding the small number of cases the percentage results tally so closely with those of Walthard and Schickele that they are at least significant.

In studying the cases of total ablation a number of observations were made which are of special interest.

Hot flushes were reported by many patients who had passed the natural menopause at the time of the operation. This fact is evidence that the ovary retains its influence as a secretory organ long after ovulation ceases. It is also confirmatory of the theory now generally accepted, that there exists in the structure of the ovary outside of the corpus luteum, an important source of its internal secretion.

There is a considerable difference of opinion as to the influence of age on the severity of artificial menopause symptoms. Polak, Dickinson, Chipman and others assert that the younger the patient is the more severe the symptoms. Walthard on the other hand finds that the age makes no difference. In our series the severest symptoms appeared most commonly in women approaching or pass-

ing through the natural menopause, that is to say between the ages of 40 and 50. This we have ascribed to the greater instability of the nervous system at the critical period of life.

In a comparison between the symptoms of the surgical and the natural menopause we find that the disturbances of the natural menopause are far more complex than in the former, ranging as they do from mild vasomotor changes to serious psychoneuroses. There is also a less definite time limit to their duration. The surgical menopause symptoms on the other hand, have a greater incidence (*i. e.*, 80 per cent. instead of 50 per cent.). Their average duration is three to four months. In general patients suffer less from the artificial than from the natural menopause.

TABLE OF STATISTICS

	Total ablation. 233 cases. Per cent.	One or both ovaries left in situ. 26 cases. Per cent.	Transplanta- tion. 53 cases. Per cent.	Chalfant transplantation. 17 cases. Per cent.
No hot flushes....	20	19	10	12
Few hot flushes ..	42	19	53	70
Many hot flushes..	38	62	37	18
Total incidence of hot flushes	80	81	90	88
Walshard	Incidence of menopause symptoms 2 per cent. less in cases of retained ovaries.			
Schickele	Incidence of menopause symptoms the same in cases of retention and ablation.			
Cemach, Sarwey, Senn	Incidence of menopause symptoms, 1 or 2 per cent. less in cases of retained ovaries.			
Konstantinidis ...	134 cases, one or both ovaries retained.			
	Vasomotor symptoms			50 per cent.
	Trophic disturbances			33½ per cent.
	Psychic disturbances			12 per cent.
Dickinson	Incidence of surgical menopause symptoms in 163 cases—one or both ovaries retained— 20 per cent.			
Tuffier	Incidence of menopause symptoms after trans- plantation, 50 per cent.			
Natural Menopause	Incidence of symptoms, 50 per cent. (Schickele).			

V. CONCLUSIONS

1. Specific surgical menopause symptoms consist chiefly of vasomotor disturbances in the form of hot flushes.

2. Theoretically, vasomotor changes of the artificial menopause are due to a break in the uteroövarian functional harmony, by which the physiological balance of the glands of internal secretion is upset with consequent dysfunctional activity.

3. After extirpation of the uterus, vasomotor disturbances ensue with approximately equal frequency, whether the ovaries be retained *in situ*, totally ablated, or transplanted.

4. Retention of ovarian tissue after hysterectomy is of little or no physiological value and may be productive of serious harm to the patient.

I am indebted to Miss H. J. Ewin, superintendent of the Free Hospital for Women, for sending letters of inquiry to patients and tabulating the answers from which the personal statistics contained in this paper were compiled.

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THE PREPARATION AND STANDARDIZATION OF OVARIAN AND PLACENTAL EXTRACTS

BY W. H. MORLEY, M. D.
Detroit, Mich.

ANYONE who has read the various articles and monographs that have appeared in the literature in the last few years on the internal secretion of the ovary or placenta has no doubt been impressed by the great disparity of results obtained with extracts of these organs. This also obtains for the other glands that possess an internal secretion with exception of the adrenals. One investigator will arrive at seemingly beautiful results with an extract of a certain endocrine gland, while another will obtain a result exactly opposite with an extract of the same gland. One investigator may isolate from the same gland two products, whose action is antagonistic. Another research worker will try to confirm the work of these others and obtain negative results, if indeed he does not get results different from those he is attempting to duplicate. The reason for this difference is that each one has made an extract by a different method and in a different way.

The need, therefore, for more uniform methods in the preparation of ovarian and placental extracts at once becomes apparent. For in no other way can the results of the different research workers and clinicians be compared. The tangible data, both in the laboratory and in the clinic,

are at best, small. At present results obtained from extracts of the entire ovary or from the yellow body alone, without note of whether aqueous, alcoholic, or ethereal extraction is employed, are reported. The results will of course vary and are not comparable. All these differences and annoyances will disappear as soon as the active principle of the ovary and placenta is isolated. But until then it would be much better if some uniform method for the preparation and the standardization of ovarian and placental extracts were formulated.

Perhaps a short review of some of the more important articles on the preparation of ovarian and placental extracts and a description of the attempts made to isolate their active principle, may be of aid in showing the absolute necessity of a more uniform method of preparation. It is only within the last ten years that an attempt has been made to isolate the active principle of the ovary and placenta, especially the former. Before that and even up to the present time, the desiccated product of the ovary or corpus luteum has been given to allay symptoms referable to some disturbance of the internal secretory mechanism of the ovary. Among the first to attempt to make an extract that would contain the active principle of the ovary was Iscovesco. He investigated, as early as 1908, the action of the so called "lipoids" obtained from the red blood corpuscles, the hyophysis, the kidney, the suprarenal capsules, the ovaries, the testicles and the corpora lutea. He found that the "lipoids" obtained from these sources exerted a certain action on the female genitalia and discovered at the same time that there were two classes of these lipoids, classified according to their action. One, which he called "homo-stimulating," had an action on the same organ from which it was derived and the other, called "hetero-stimulating," had an action on different organs. This division was purely arbitrary, as he discovered later.

Of special importance are the two "lipoids" which he characterizes as "II F. b." and "V. D. c.," both being obtained from the ovary, the latter he was able to isolate from the corpora lutea. His technique in preparation as given in his paper, which appeared in the *Comptes Rendus de Soc. de Biol.*, 1912, lxxii, 858, is, briefly, as follows: The fresh organ is finely pulped and the pulp thrown into three times its volume of 95 per cent. alcohol, in which it is allowed to remain two hours. This is then filtered, set aside to extract the lipoids and is designated as Fraction I. The residual pulp is desiccated at 40 degrees, pulverized and treated with different solvents. First, it is extracted with sulphuric ether and this is called Fraction II of the "lipoids." The residue therefrom is dried, powdered and treated with acetone in the same manner, which gives Fraction III. Further extraction with the resulting residue gives Fraction IV, and, lastly, with alcohol, Fraction V is obtained. All these fractions being prepared, their subdivision and purification follows. For example, with Fraction II the ether extract is dissolved in petroleum ether, giving an insoluble portion A, which is small in amount, and a soluble portion B, which constitutes the major part. This latter is desiccated and redissolved in ether. There remains then an insoluble part, which is removed by the centrifuge. The clear supernatant solution is then thrown into about ten times its volume of acetone, pure and free from any acid, and allowed to stand in the refrigerator 24 hours. At the end of this time an abundant precipitation will be found in the bottom of the receptacle, which, when filtered, constitutes portion C. The acetone solution is concentrated and put into the refrigerator, giving, after cooling, a yellowish white mass, which is portion D. The remainder of the acetone solution, which has passed through the filter, is then completely dried and the precipitate is dissolved in boiling alcohol. All should dissolve, after which it is cooled for 24 hours, giving portion E, and a dissolved portion F. Each of these fractions (A, B, C, D, E, and F), thus isolated, is far from being considered as chemically pure and each must be dissolved in petroleum ether, ordinary ether, cold alcohol, and finally in warm alcohol. There is obtained by this means the series a, b, c, d of the corresponding substances. The same procedure is gone

through with Fractions III, IV and V. Each fraction was tested upon animals, and only those which produced a rapid growth of the uterus were considered "active."

Thus it will be seen from the careful and painstaking work of Iscovesco that when an extract of the ovary, corpus luteum or of the placenta is used in laboratory experiments or in the clinic, care must be exercised in obtaining the active fraction of the extract or the vital part of the organ may be left behind on the filter paper and thrown away. Concerning the physiological action of these fractional extracts of Iscovesco and the results obtained by him in the laboratory and in the clinic, no mention will be made. Those interested in this part of his work, may consult his recent articles in literature.

According to his technique, outlined above, the "active substance," which he describes as "II F. b.," might briefly be considered as an ether extract of the desiccated organ (ovary), soluble in acetone (at ordinary temperature), having further been purified by boiling alcohol, concentration and extraction with petroleum ether. The other substance, V. D. c., appears to have been obtained from the residue remaining after treating first with alcohol, then with ether, then with acetone, followed by chloroform, and finally with alcohol again. This alcohol soluble substance is then presumably purified by solution in petroleum ether, resolution in ether and precipitation by acetone and in turn further purified by solution in petroleum ether, ordinary ether and cold alcohol. The substance then is acetone insoluble, whereas his previous substance II F. b. is soluble in acetone.

Herrmann followed the plan of Iscovesco in the preparation of ovarian and placental extracts and published his article early in 1915. Herrmann believes that he has succeeded in separating the "active substance" of the corpus luteum and of the placenta as a specific chemical substance. He attempted to prove this clinically and on ani-

mals. Many colored figures are appended to his article and his results, if true, show wonderful changes from only a few doses of his so-called "active principle."

His method of extraction, while not identical with that of Iscovesco, given above, will not be described *in toto* at this time. He was able to obtain three fractions by his method and these were further purified by distillation and tested. It was found that the so-called middle run produced a thickly viscous body, which represents, as he believes, the real active principle of the ovary. This active substance, as further described by Herrmann, is a yellowish glistening oil, which is solidified by cooling, but otherwise remains thickly viscous. It gives a very decided cholesterin reaction. It becomes brown when exposed to the air, apparently by taking up oxygen, and is composed of three elements, carbon, hydrogen and oxygen. The body is a cholesterin derivative. It is soluble in alcohol, ether, petroleum ether, acetone and benzol, but is insoluble in water.

Herrmann found the same active substance with identical physiological properties, in the placenta, as well as in the corpus luteum. However, one placenta contains more of the active substance than one corpus luteum. The method of preparation is the same in both cases.

Seitz, Wintz and Fingerhut found that the corpus luteum contained two "bodies." One, which they designated as "luteo lipoid," has an inhibitory action on the blood and, injected subcutaneously, before and during the menses, lessens the flow and shortens it. The other body they call "lipamin," soluble in water, a luteo lipoid or lecithin-albumin, which causes, when injected into animals, an increased growth of the genitalia. Subcutaneously injected in women, it causes the appearance of the menses in cases of amenorrhea. "Luteo lipoid" and "lipamin" are antagonistic bodies and regulate the course of the menses. Their method of extraction is given in an indefinite sort of way. They obtain the various lipoid fractions by extraction with alcohol, chloroform, ether and acetone. By later evaporation, redissolving and extraction they obtained the two antagonistic bodies mentioned above.

A hasty review of the methods of these research workers (Iscovesco, Herrmann, Seitz *et al.*) shows that they all used practically the same method of extraction and, as far as can be gleaned from their clinical and experimental reports, they arrived at about the same results. However, the difference may be due to the fact that Herrmann obtained his so-called active substance in a purer state. These investigators at least used a certain definite method of extraction and their resulting products could be tested experimentally and clinically with a view of producing certain definite physiological and anatomical results.

Other workers, who have reported results obtained with ovarian or placental extracts, have been too prone to give the clinical results secured with, what they loosely call, an "extract." This may be an aqueous, alcoholic or ethereal extract or, as often happens, it is not an extract at all but simply the dried gland in the form of a desiccated powder. It should be clearly borne in mind that the kind of extract must be mentioned if the work is to prove of any value to others. A qualifying adjective such as "ethereal," "aqueous," if properly employed, may sufficiently designate the method of preparation. Not only is uniformity of preparation desirable, but some form of standardization of the resulting products is necessary to obtain extracts of the same strength and action. Many of the failures to produce the desired effect are due to a lack of proper standardization of an otherwise perfect product.

In order to perfect a proper preparation and later a suitable method of standardization, some research work was undertaken by the writer during the last two years. Up to the present time it can definitely be stated that no ideal method of preparation has been formulated and, until that is accomplished, the standardization of the product will not be attempted. Various forms of extracts of ovary, of corpus luteum, of the ovary minus the corpus luteum (ova-

rian residue) have been made by exact chemical methods and the resulting extract tried on animals. The results have all been negative. One extract, a powder soluble in water, has been obtained and clinically it has seemed to be active in some conditions, *i. e.*, disturbances of the artificial or the physiological menopause. But, in this connection, the results are too vague, ephemeral and transitory; hence conclusions drawn therefrom, do not have much value.

For example, a few ampules of the soluble extract are given or sent to Doctor A., with the request that he try its action upon the disturbances of the menopause when a suitable case presents itself. Later Doctor A. has a patient who "says" that she is suffering from "flashes of heat," "insomnia," etc. Doctor A. makes an examination and finds no pelvic pathology. But upon the statement of the patient he injects an ampule of the soluble corpus luteum. In a day or two he repeats the injection. After a few injections Doctor A. "asks" the patient if she is feeling better, and the patient, not wishing to offend Doctor A., or thinking that she does feel better, answers in the affirmative. Doctor A. continues the treatment and later reports this case as one cured.

Results, based upon the statement of the patient, must be considered with extreme care. Yet that, practically, today is all the data upon which judgment can be passed as to whether a preparation or extract of the ovary has any therapeutic action. There are many factors in the preparation of an extract which may have an important bearing upon its therapeutic activity, such as the freshness of the material, the purity of the chemicals, proper temperature, avoidance of very high or very low degrees of heat or cold. Variations in all or any of these may tend to render the resulting extract inert or cause it to produce results, that are due to faulty preparation.

In this connection mention will be made of Rosenheim, who reported his work on the pressor principles of pla-

cental extracts. Rosenheim was attempting to confirm the work of Dixon and Taylor, who claimed that alcoholic extracts of human placenta contained substances which, on intravenous injection, produced a rise of the blood-pressure and a contraction of the pregnant uterus.

Dixon and Taylor's method of preparing these extracts consisted in mincing fresh human placenta, covering it with absolute alcohol and filtering after some time. The filtrate was evaporated and again taken up with absolute alcohol. The residue of the last extract, dissolved in saline solution, was injected intravenously. Rosenheim thought that the effect of the injections seemed to suggest the presence of adrenalin or a similar substance. Trying to prove this, he found that the active principle was not identical with adrenalin. Rosenheim made alcoholic extracts in several ways, and found that the normal human placenta did not contain any pressor principle. Next he made three different extracts, as follows: In the first the fresh minced placenta was barely covered with alcohol to allow putrefaction to take place; in the second the fresh minced placenta was shaken up with one liter of saline solution saturated with chloroform and kept for four days at room temperature; and in the third, the fresh minced placenta was mixed with absolute alcohol (1000 c.c. of minced material to one liter of absolute alcohol). Rosenheim found that the first extract (above) contained a strong pressor principle, while the second and third did not, or, to quote his table:

CONDITIONS OF EXPERIMENT.	RESULT.
A. (No. 1 above) Extract after free putrefaction.	Strong pressor effect.
B. (No. 2 above) Extract after autolysis alone.	Total absence of pressor effect.
C. (No. 3 above) Extract of fresh organ.	Total absence of pressor effect.

Rosenheim was later able to identify this pressor principle of Dixon and Taylor as belonging to the amines and it probably is derived from the amino acids (leucine and tyrosine), the cleavage products of proteins.

Barger and Walpole came to practically the same conclusions in their work upon putrid meat, *i. e.*, that it contains a pressor principle.

Five extracts of the placenta were prepared by the

writer and their action tested on the blood-pressure and upon the isolated uterus, as well as by injection into animals (rabbits). These extracts were prepared as follows:

Number one was an aqueous extract obtained by exposing the minced placenta to distilled water, slightly acidulated. The resulting fluid was boiled with acetic acid to precipitate the coagulated proteins, filtered, evaporated and distilled water added to bring it up to its original volume. This solution was passed through a Berkfeldt filter and filled into 1 c. c. sterile ampules.

Number two was obtained by placing in a wide-mouthed bottle 725 gm. of minced placenta pulp. This mixture was allowed to stand at room temperature for four days, loosely corked. Then 725 c.c. sterile distilled water added, mixed and filtered and the filtrate boiled with acetic acid. This was filtered while hot, and the filtrate cooled and evaporated to more than one-half its volume. Sterile distilled water was added to bring the amount up to 725 c.c., the original volume. This latter was next passed through a Berkfeldt filter and filled into 1 c.c. sterile ampules.

Number three was prepared by taking 400 gm. of minced placental pulp and adding to it 400 c.c. of normal salt solution, saturated with chloroform. This was loosely corked and allowed to stand at room temperature for four days. It was then filtered and the filtrate boiled with acetic acid to precipitate the coagulated proteins. This was again filtered while hot, cooled and evaporated to less than one-half its volume. Sterile distilled water was added to bring the amount up to 400 c.c., the original volume. It was then passed through a Berkfeldt filter and filled into 1 c.c. sterile ampules.

Number four was prepared by adding 400 c.c. of absolute alcohol to 400 gm. of minced placental pulp. This was allowed to stand for some time at room temperature in bottle loosely corked. Then the whole was filtered, the filtrate boiled with acetic acid, filtered through paper and evaporated to less than half of its volume. Sterile distilled water was added to make 400 c.c., the original amount. This was passed through a Berkfeldt filter and filled under sterile conditions into 1 c.c. sterile ampules.

Extract number five was made by taking about 500 gm. of minced placental pulp, which was placed in a large-mouthed bottle. This was allowed to stand in the incubator, loosely corked, for several days. The mixture was shaken every two or three days. Then it was filtered and treated as the others (Nos. 1-4) and filled into sterile 1 c.c. ampules.

These five extracts were submitted to Mr. L. W. Rowe to be tested on the isolated uterus of the guinea-pig and upon the blood-pressure of a chloretonized dog. Mr. Rowe reported as follows: all five extracts contracted the isolated uterus of the virgin guinea-pig, when administered in sufficient quantity. About 0.25 c.c. of the undiluted sample was necessary in each case to produce an appreciable contraction. The action of number five (5) and number two (2) seemed a little stronger than that of the others, and this was due to the fact that these extracts were partly decomposed. All meat extracts will contract the isolated uterus if they are sufficiently concentrated and this action is more marked if decomposition or partial decomposition has taken place.

The effect of these extracts upon the blood-pressure was not very marked nor characteristic. In most instances the blood-pressure fell slightly, but this was more marked with number five (5), which action was no doubt due to the very evident decomposition of this sample. The results of these tests indicate that placental extracts do not contain a pressor or marked oxytocic principle.

The action of these extracts (Nos. 1-5) upon animals, when injected intraperitoneally, was negative. A large number of injections produced no macroscopic effect upon the internal or external genitalia of the animals injected. There was no anatomical difference between them and the control animals.

From a review of the more recent literature, from the

animal experiments thus far undertaken with extracts of the corpus luteum, ovary and placenta, and from the different methods employed in making these extracts, the following conclusions seem justifiable.

1. A more uniform method of preparing extracts must be instituted.

2. Some method for the standardization of these extracts must be discovered, in order to facilitate the comparison of the results of the different laboratory workers and clinicians.

3. Many results obtained in the laboratory or in the clinic are due to the faulty preparation of extracts.

4. The isolation of the active principle of the ovary and the placenta will clear up many, if not all, of these mooted points.

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THE PLACENTA REGARDED AS A GLAND OF INTERNAL SECRETION

BY ROBERT T. FRANK, M. D.

New York

FROM the days of antiquity it has been known that the placenta acts as intermediary between the maternal organism and the fetus. Only in recent years, however, has another function been ascribed to this organ, namely, that of a gland of internal secretion. The first comprehensive expression of this view was published in 1905 by Halban.

1. HALBAN'S THEORY. Joseph Halban¹ published an elaborate paper entitled "Die innere Sekretion von Ovarium und Placenta und ihre Bedeutung für die Funktion der Milchdrüse." The author based most of his deductions upon the interpretation of clinical facts, some of them from his own experience, others gathered from various sources, though not a few of the gaps in his evidence were bridged by facts obtained from animal experimentation. The work of many investigators, performed during the last decade, has confirmed and elaborated many of the deductions made by Halban, and has placed the major part of his hypothesis upon a firm basis of fact. The following is a brief résumé of Halban's theory.

Both the puberty impulse (growth) and the menstrual stimulus to the uterus and breasts (in the breast, monthly swelling, colostrum formation, vicarious menstruation noted in virgins) are derived from the ovaries. Though the initial

pregnancy impulse is originated by the ovum,* breast hypertrophy and later milk secretion is not interfered with by castration during pregnancy. On the other hand, both uterus and breasts continue their hypertrophy after fetal death, or during the growth of a hydatid mole without fetus. Consequently, it must be the placenta (fetal trophoblast or chorionepithelium) and not the fetus which elaborates the pregnancy growth substance.

The fetus of both sexes becomes sensitive to the placental stimulus in the eighth and ninth months of intra-uterine life. This is shown by hyperplasia of uterus and breasts in females, and of prostate and breasts in males (Bayer,³ Schlachta⁴). The genital hemorrhages noted in new-born female infants (occurring in 0.35 per cent.), Schukowski⁵ a few days postpartum are due to the sudden withdrawal of the placental stimulus, as is the puerperal involution of uterus and prostate, which reaches its completion about three weeks after birth.

That the placental influence is a chemical stimulus acting by way of the blood stream and not a direct local stimulation is proved by the uterine reaction which occurs in ectopic pregnancy.

From these observations Halban concludes *that the chemical products of both the ovary and of the placenta produce hyperemia and uterine menstrual (or decidual) reaction, and that both likewise exert an influence on the breasts.* He further draws the deduction, unwarranted by his evidence, that liver changes in eclampsia, etc., are due to placental influences, and *that the ovary during pregnancy loses its trophic protective power over the genitals, its function being vicariously assumed by the placenta.*

2. INFLUENCE OF PLACENTAL EXTRACTS ON UTERUS AND BREASTS. Before attempting an analysis of Halban's theorems, it will be best to present what is known today of

* In the uterus this certainly does not hold good. The work of Leo Loeb² has shown that the chemical action of the corpus luteum plus the local uterine irritation exerted by any foreign body (or by injury to the uterine mucosa) can produce the uterine reaction. Various authors have also elicited massive breast hyperplasia by means of corpus luteum extracts alone.

the action of the placenta *per se*, unclouded by any possible ovarian influence. Thus, most simply, can be demonstrated the evidence upon which the placenta can be called a gland of internal secretion. The earlier experimental work, as that of Claypon and Starling,⁶ Foa⁷ and Basch⁸ who used weak aqueous extracts of homologous or heterologous placenta can be dismissed as inconclusive.⁹

Iscoveseo,^{* 10} Fellner,¹¹ Aschner,¹² Seitz, Wintz and Fingerhut,¹³ Herrmann,¹⁴ Frank and Rosenbloom,¹⁵ however, employed the concentrated fat soluble fraction of placental extracts which produces a strong and unmistakable reaction.

Subcutaneous injections of either aqueous or saline emulsions of the lipid, or solutions in oils or alcohol cause enormous and rapid hyperplasia of the uterus. Both mucosa and musculature participate in the increase. This effect is obtained within 6 to 8 days in castrated animals, where ovarian influence can be definitely excluded. Rabbits, guinea-pigs and rats show the same reaction. Similar though less marked effects are produced through introduction of the extract by mouth.[†]

A similar and equally rapid hyperplasia is exerted upon the breasts of rabbits. The nipples increase in size, the glandular tissue hypertrophies. If the stimulus is prolonged, colostrum can be expressed. The breast of the rat and guinea-pig is less susceptible.

The uterus and breasts of these laboratory animals (rabbits are to be preferred because the breast reaction, which can be followed without at once sacrificing the ani-

* Although Iscoveseo used only ovarian extracts, his work should be considered the basis of all the investigations that followed. The similarity of corpus luteum and placental lipoids will be emphasized in a succeeding paragraph.

† The weight of the uterus compared with the weight of the uterus of a normal control animal of the same body weight may reach 5 to 9 times that of the control.

mal, is most plainly evidenced in rabbits), furnish a reliable biological test for testing the potency of the extracts.

3. CHEMISTRY. Our knowledge of the chemical composition of placental extracts is in a state of chaos. Iscovesco (l. c.) working with ovarian extract devised a complicated method of purification based upon elective solubility in various fat solvents. Herrmann, using corpus luteum and placental material (l. c.) published a still more complicated method depending upon extraction in vacuo, elective solubility, and fractional distillation with superheated steam. Neither of these authors, judging by our experiences (*vide infra*), appear to have obtained a substance free from impurities.

The writer successively in conjunction with three biological chemists (Dr. J. Rosenbloom (l. c.), Mr. O. I. Lee, and now with Mr. P. M. Giesy) has for the last two and one-half years been engaged in attempting to isolate the active principle. Our attempts have not been crowned with success.

The knowledge obtained to date by our investigation may be summarized by stating that the potent crude extract which is obtained by continuous extraction with alcohol, is a dark, semi-liquid mixture which resists high degrees of heat (350° C.), strong acids or alkalies and saponification without loss of potency. It either oxydizes or polymerizes on standing, gradually losing its activity. It is fully soluble in 95 per cent. alcohol, partially so in chloroform, ether, oils and in benzine (the active fraction at times following the benzine insoluble portion). The activity persists after removal of cholesterin and indol, which may be regarded as contaminations. The active substance has not been sufficiently purified to permit of analysis. Our attempts to duplicate Herrmann's work leads us to conclude that his final product was a mixture and not a single compound.

4. SIMILARITY OF CORPUS LUTEUM AND PLACENTA. In agreement with Herrmann (l. c.) we have found that the active principles obtained from the corpus luteum and from the placenta can be extracted by identical methods, chemically have identical properties and biologically produce identical results upon the uterus and breasts. Although the quantitative yield from corpus luteum is far richer than from the placenta, placental material (human) is so much more readily obtained in large amounts, that we have mainly used the latter in our work.

Whether the two are merely similar, or are identical cannot be decided until both are isolated as chemical entities, unless clear cut specific differences in physiological action can be shown. No such differences in action have as yet been discovered.

5. NEW PHYSIOLOGICAL FACTS. (a.) Placental extract causes hyperplasia of transplanted portions of the uterus, as well as in the uterus left in situ.

(b.) The action is not diminished by removal of the adrenals, pancreas or thyroid, or combined removal of thyroid and adrenals.

(c.) The ovaries are not stimulated by the extract.

(d.) The atrophic uterus of castrated animals responds readily to the stimulus of the placental extract, even after long periods of time have elapsed. (The longest period was 16 months after castration.)*

6. SOURCE OF THE PLACENTAL HORMONE. The main function of the placenta unquestionably pertains to the exchange of nutrient substances from the mother to the fetus, and to the elimination of waste products of the fetus in a reverse direction. The fulfilment of this function accounts sufficiently for the histological structure of the

* Details of the preceding experiments will be published in a subsequent article.

placenta, which is characterized by a labyrinth of sinuses lined by fetal cells. Therefore, it does not follow in this instance, because an intimate relationship between blood channels and cellular components exists, a distribution usually characteristic of glands of internal secretion, that the placenta must be a ductless gland. If, further, the apparent identity of composition and action of corpus luteum and placental secretion is considered, and the well-known abhorrence of the organism to unnecessary duplication of function is kept in view, the question may logically be propounded whether the placenta does not act merely as a storage reservoir for the active principle elaborated by the corpus luteum during the earlier part of pregnancy. During the latter half of gestation the yellow body histologically has the appearance of an involuting functionless gland. No proof in substantiation of this hypothesis can as yet be adduced.

SUMMARY

1. The experimental work of the last decade proves that Halban was correct in ascribing to the placenta an action upon the uterus and breasts.

2. Placental extracts (mainly the lipid fraction) rapidly induce hyperplasia of the uterus and breast (gland tissue and nipples), in castrates or in non-castrated animals.

3. The chemical substance which induces these changes is thermostabile, very resistant to strong alkalies and acids, and completely soluble in 95 per cent. alcohol.

4. The substance appears identical in its physical, chemical and biological properties with a similar substance obtained from the corpus luteum.

5. The substance can exert its influence in the absence of the thyroids, adrenals, pancreas, or in the absence of thyroid and adrenals combined.

6. In view of the apparent identity of corpus luteum and placental substance the question arises whether the placenta acts merely as a storage reservoir for corpus luteum secretion during the latter half of pregnancy, or whether the placenta elaborates a hormone of its own.

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